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(54) Title: DRY POWDER INHALERS, RELATED BLISTER DEVICES, AND ASSOCIATED METHODS OF DISPENSING DRY POWDER SUBSTANCES AND FABRICATING BLISTER PACKAGES

(57) Abstract: THE PRESENT INVENTION INCLUDES DRY POWDER INHALERS AND ASSOCIATED MULTI-DOSE DRY POWDER PACKAGES FOR HOLDING INHALANT FORMULATED DRY POWDER SUBSTANCES. THE MULTI-DOSE PACKAGE (100) COMPRISES AT LEAST ONE THIN PIEZOELECTRIC POLYMER MATERIAL LAYER (28) DEFINING AT LEAST A PORTION OF A PLURALITY OF SPATIALLY SEPARATED DISCRETE ELONGATE DRY POWDER CHANNELS (101) HAVING AN ASSOCIATED LENGTH, WIDTH AND HEIGHT; AND A METALLIC MATERIAL (100M) ATTACHED TO SELECTED PORTIONS OF THE PIEZOELECTRIC POLYMER MATERIAL (28) INCLUDING EACH OF THE REGIONS CORRESPONDING TO THE ELONGATE DRY POWDER CHANNELS (101) TO, IN OPERATION, DEFINE ACTIVE ENERGY RELEASING VIBRATORY CHANNELS. IN OPERATION, THE ELONGATE CHANNELS CAN BE SELECTIVELY INDIVIDUALLY ACTIVATED TO VIBRATE UPON EXPOSURE TO AN ELECTRICAL INPUT. THE DRY POWDER INHALER (10) INCLUDES AN ELONGATE BODY (10B) HAVING OPPOSING FIRST AND SECOND OUTER PRIMARY SURFACES (11, 12) WITH A CAVITY (10C) THEREBETWEEN AND A MULTI-DOSE SEALED BLISTER PACKAGE (100) LOCATED IN THE SAID CAVITY (10C). THE INHALER (10) ALSO INCLUDES A COVER MEMBER (15) THAT IS PIVOTABLY ATTACHED TO THE ELONGATE BODY (10B).

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# DRY POWDER INHALERS, RELATED BLISTER DEVICES, AND ASSOCIATED METHODS OF DISPENSING DRY POWDER SUBSTANCES AND FABRICATING BLISTER PACKAGES

## Related Applications

This application claims the benefit of priority to U.S. Provisional Application Serial No. 60/379,521, filed May 10, 2002, U.S. Provisional Application Serial No. 60/392,671, filed June 27, 2002, and U.S. Patent Application Serial No. 60/440,513, filed January 16, 2003, the contents of which are hereby incorporated by reference as if recited in full herein.

## Field of the Invention

The present invention relates to the delivery of dry powder substances, such as dose-regulated pharmaceutical products, as inhalant aerosols.

## Background of the Invention

Dry powder inhalers (DPI's) represent a promising alternative to pressurized pMDI (pressurized meted dose inhaler) devices for delivering drug aerosols without using CFC propellants. *See generally*, Crowder et al., *2001: an Odyssey in Inhaler Formulation and Design*, Pharmaceutical Technology, pp. 99-113, July 2001; and Peart et al., N*ew Developments in Dry Powder Inhaler Technology*, American Pharmaceutical Review, Vol. 4, n.3, pp. 37-45 (2001). Typically, the DPIs are configured to deliver a powdered drug or drug mixture that includes an excipient and/or other ingredients. Conventionally, many DPIs have operated passively, relying on the inspiratory effort of the patient to dispense the drug provided by the powder. Unfortunately, this passive operation can lead to poor dosing uniformity since inspiratory capabilities can vary from patient to patient (and sometimes even use-to-use by the same patient, particularly if the patient is undergoing an asthmatic attack or respiratory-type ailment which tends to close the airway).

Generally described, known single and multiple dose dry powder DPI devices use: (a) individual pre-measured doses, such as capsules containing the drug, which can be inserted into the device prior to dispensing; or (b) bulk powder reservoirs which are configured to administer successive quantities of the drug to the patient via a dispensing chamber which dispenses the proper dose. *See generally* Prime et al., *Review of Dry Powder Inhalers*, 26 Adv. Drug Delivery Rev., pp. 51-58 (1997); and Hickey et al., *A new millennium for inhaler technology*, 21 Pharm. Tech., n. 6, pp. 116-125 (1997).

In operation, DPI devices desire to administer a uniform aerosol dispersion amount in a desired physical form (such as a particulate size) of the dry powder into a patient's airway and direct it to a desired deposit site. If the patient is unable to provide sufficient respiratory effort, the extent of drug penetration, especially to the lower portion of the airway, may be impeded. This may result in premature deposit of the powder in the patient's mouth or throat.

A number of obstacles can undesirably impact the performance of the DPI. For example, the small size of the inhalable particles in the dry powder drug mixture can subject them to forces of agglomeration and/or cohesion (*i.e.*, certain types of dry powders are susceptible to agglomeration, which is typically caused by particles of the drug adhering together), which can result in poor flow and non-uniform dispersion. In addition, as noted above, many dry powder formulations employ larger excipient particles to promote flow properties of the drug. However, separation of the drug from the excipient, as well as the presence of agglomeration, can require additional inspiratory effort, which, again, can impact the stable dispersion of the powder within the air stream of the patient. Unstable dispersions may inhibit the drug from reaching its preferred deposit/destination site and can prematurely deposit undue amounts of the drug elsewhere.

Further, many dry powder inhalers can retain a significant amount of the drug within the device, which can be especially problematic over time. Typically, this problem requires that the device be disassembled and cleansed to assure that it is in proper working order. In addition, the hygroscopic nature of many of these dry powder drugs may also require that the device be cleansed (and dried) at periodic intervals.

Some inhalation devices have attempted to resolve problems attendant with conventional passive inhalers. For example, U.S. Patent No. 5,655,523 proposes a dry powder inhalation device which has a deagglormeration/aerosolization plunger rod or biased hammer and solenoid, and U.S. Patent No. 3,948,264 proposes the use of a battery-powered solenoid buzzer to vibrate the capsule to effectuate the release of the powder contained therein. These devices propose to facilitate the release of the dry powder by the use of energy input independent of patient respiratory effort. U.S. Patent No. 6,029,663 to Eisele et al. proposes a dry powder inhaler delivery system with a rotatable carrier disk having a blister shell sealed by a shear layer that uses an actuator that tears away the shear layer to release the powder drug contents. The device also includes a hanging mouthpiece cover that is attached to a bottom portion of the inhaler. U.S. Patent No. 5,533,502 to Piper proposes a powder inhaler using patient inspiratory efforts for generating a respirable aerosol and also includes a rotatable cartridge holding the depressed wells or blisters defining the medicament holding receptacles. A spring-loaded carriage compresses the blister against conduits with sharp edges that puncture the blister to release the medication that is then entrained in air drawn in from the air inlet conduit so that aerosolized medication is emitted from the aerosol outlet conduit. The contents of these patents are hereby incorporated by reference as if stated in full herein.

More recently, Hickey et al. in U.S. Provisional Application Serial No. 60/188,543 and corresponding international PCT patent publication WO 01/68169A1 have proposed a DPI system to actively facilitate the dispersion and release of dry powder drug formulations during inhalation using piezoelectric polymer film elements which may promote or increase the quantity of fine particle fraction particles dispersed or emitted from the device over conventional DPI systems: the contents of these documents are hereby incorporated by reference as if recited in full herein.

Notwithstanding the above, there remains a need to provide easily used, cost effective, and reliable dry powder inhalers.

## Summary of the Invention

Embodiments of the present invention provide improved dry powder inhaler configurations. The dry powder inhalers may be particularly suitable for use with active piezoelectric polymer-driven dispersion or delivery means. Embodiments of

the present invention are directed to dry powder inhaler configurations and associated receptacle or blister packages as well as methods for dispensing dry powder substances and/or methods for fabricating blister packages.

In certain embodiments, the dry powder inhaler can be pre-packaged with an integrated predetermined quantity of individually dispensable doses that is disposable after a desired dispensing period, such as 30, 60, or 90 days. This can limit the amount of patient or user interchange with the dry powder inhaler, thereby removing the requirement that the DPI be disassembled to insert additional doses into the unit (and may also promote a more hygienic product). In other embodiments, the DPI can be configured to allow replaceable dry powder packages to be inserted/removed from the device at desired intervals.

In particular embodiments, whether the inhaler is disposable at each refill interval or refillable and reusable, the dry powder package therein can include a thin layer of piezoelectric polymer material that is in communication with each of a plurality of selectively excitable receptacle regions. In operation, the piezoelectric polymer material layer is rapidly flexed back and forth to deform a selected receptacle(s) region, thereby actively facilitating the dispersal of the dry powder drug into the inhalation delivery path.

The active piezoelectric regions can be formed as an elongated resonant chamber to cause the dry powder substance to contact the floor and/or ceiling of the resonant chamber repeatedly. This can increase the transfer of energy from the actively flexing piezoelectric polymer resonant chamber to the dry powder substance, promoting longer contact times therewith as the dry powder substance travels the length of the resonant chamber and exits the patient inhalation port.

The increased active dispersal can promote resonance of the dry powder substance and allow improved blends, such as increased concentrations and/or reduced total quantities of substances relative excipient, over conventional dry powder pharmaceutical substances.

Certain embodiments of the present invention are directed to multi-dose dry powder packages for holding inhalant formulated dry powder substances. The packages comprise: (a) a platform body comprising a plurality of sealed blisters thereon and at least one thin piezoelectric polymer material layer forming at least a portion of each of the sealed blisters, wherein the sealed blisters comprise a respective

at least one of a plurality of spatially separated discrete elongate dry powder channels having an associated length, width and height; and (b) a conductive material attached to selected portions of the piezoelectric polymer material to, in operation, define active energy-releasing vibratory channels, and wherein, in operation, the elongate channels can be selectively activated to vibrate upon exposure to an electrical input.

Other embodiments of the invention are directed to dry powder inhalers. The inhalers include: (a) an elongate body having opposing first and second outer primary surfaces with a cavity therebetween and having opposing top and bottom end portions; (b) a multi-dose sealed blister package holding a plurality of discrete meted doses of a dry powder inhalable product located in the cavity of the elongate body; (c) an inhalation port formed in the bottom end portion of the elongate body, the inhalation port configured to be in fluid communication with at least one of the discrete meted doses during use; and (d) a cover member that is pivotably attached to the elongate body so that it remains attached to the body during normal operational periods of use and moves to a first closed position to overlie the inhalation port at the bottom end portion of the body during periods of non-use and moves to a second open position away from the inhalation port during periods of use to allow a user to access the inhalation port.

The cover member may have a length that is greater than a major portion of the length of the elongated body and a width is less than the width of the elongate body. In certain embodiments, the cover member has two opposing first and second end portions, the first end portion being pivotably attached to the upper portion of the elongated body with the cover having a major portion with a substantially planar profile and a downwardly extending arcuately shaped second end portion.

Still other embodiments of the present invention are directed to methods for fabricating a multi-dose disposable dry powder blister package. The method includes: (a) providing a piezoelectric polymer material; (b) concurrently forming a plurality of elongated projections having a width and an associated length into the piezoelectric polymer material; and (c) applying a metallic material to selected regions of at least one primary surface of the piezoelectric polymer material so as to cover at least a portion of each of the plurality of projections.

Another embodiment of the invention is directed to methods of administering an inhalable dry powder product to a subject. The method includes: (a) oscillating a

piezoelectric polymer material forming at least a portion of a sealed encased elongated channel and having opposing first and second end portions at a selected frequency or frequency range; (b) disrupting the integrity of the seal associated with the elongated channel at a second end portion; (c) directing a dry powder product to flow through the elongated channel to exit at the second end portion so that a major portion of the dry powder substance repeatedly contacts the oscillating piezoelectric material at a plurality of locations along the elongated channel; (f) imparting energy to the dry powder product based on the oscillating and directing steps to cause the dry powder product to vibrate to generate an inhalable aerosol; and (g) releasing the inhalable aerosol to a subject upon inhalation.

Still other embodiments are directed toward methods of administering an inhalable dry powder product to a subject. The methods include: (a) providing an inhaler with a multiple dose blister package comprising piezoelectric polymer material that is associated with a plurality of discrete sealed blisters holding respective dry powder doses; (b) priming a selected portion of the package to vibrate the dry powder in at least one selected sealed blister proximate in time to an intended inhalation delivery thereof; then (c) introducing an opening in the at least one selected blister; (d) vibrating the at least one selected blister by a applying an input signal to the piezoelectric polymer material proximate the selected blister; and (e) releasing the inhalable dry powder to a subject upon inhalation.

These and other objects and/or aspects of the present invention are explained in detail in the specification set forth below.

## Brief Description of the Drawings

**Figure 1** is a top view of a dry powder inhaler according to embodiments of the present invention.

**Figure 2** is top perspective view of the dry powder inhaler shown in **Figure 1**.

**Figure 3** is a side perspective view of the dry powder inhaler shown in **Figure 1**.

**Figure 4** is a side perspective view similar to that shown in **Figure 3**, but illustrating the cover member in an open position.

**Figure 5** is another side perspective view of the device shown in **Figure 1** with the cover in an open position.

**Figure 6** is a bottom view of the device shown in **Figure 1**, with the cover open as shown in **Figure 4**.

**Figure 7** is a greatly enlarged partial top view of the device shown in **Figure 1** with the cover open as shown in **Figure 4**.

**Figure 8** is an exploded view of the device shown in **Figure 1**.

**Figure 9** is a schematic top view of a multi-dose dry powder package according to embodiments of the present invention.

**Figure 10A** is a section view of the package of **Figure 9** taken along line **10A-10A** thereof according to embodiments of the present invention.

**Figure 10B** is a section view similar to that shown in **Figure 10A** but with the well having an alternate configuration according to embodiments of the present invention.

**Figure 11** is a top view of an alternate dry powder multi-dose package according to certain embodiments of the present invention.

**Figure 12A** is a perspective view of a stacked configuration of dry powder multi-dose packages according to embodiments of the present invention.

**Figure 12B** is a side edge view of the configuration shown in **Figure 12A**.

**Figure 12C** is a schematic view of a portion of a blister package according to embodiments of the present invention.

**Figure 13** is a front perspective view of a scrolled configuration of a dry powder multi-dose package according to alternate embodiments of the present invention.

**Figure 14A** is a side perspective view of an undulated multi-dose package according to still other embodiments of the present invention.

**Figure 14B** is a top perspective view of the device shown in **Figure 14A**.

**Figure 15A** is a top view of an alternate embodiment of a dry powder inhaler shown in an open position according to embodiments of the present invention.

**Figure 15B** is a side view of the device shown in **Figure 15A** with the device in a closed position.

**Figure 15C** is a top view of a multi-dose dry powder package suitable for use in the device shown in **Figure 15A** according to embodiments of the present invention.

**Figure 16A** is a graph of the vibration amplitude/frequency input used to disperse the dry powder to a patient according to embodiments of the present invention.

**Figures 16B-16D** are schematic illustrations of three different dry powders and associated customized non-linear powder specific input signals according to embodiments of the present invention.

**Figure 17A** is a side section view of a blister package with a powder release (which may be a slit or puncture) member according to embodiments of the present invention.

**Figure 17B** is a side section view of the blister package shown in **Figure 17A** after the bottom forward portion (in the flow direction) of the blister has been opened according to embodiments of the present invention.

**Figure 18A** is a perspective top view of a multi-dose package according to embodiments of the present invention.

**Figure 18B** is a top view of the package shown in **Figure 18A**.

**Figure 18C** is a bottom view of the package shown in **Figure 18A** according to embodiments of the present invention.

**Figure 18D** is a partial bottom perspective view of the package shown in **Figure 18C**.

**Figure 18E** is a top perspective view of the package shown in **Figure 18A** illustrated without the covering of the package according to embodiments of the present invention.

**Figure 19A** is a side section view of a blister package with a top positioned powder release member according to other embodiments of the present invention.

**Figure 19B** is a side section view of the blister package shown in **Figure 19A** after a top portion of a blister has been opened according to embodiments of the present invention.

**Figure 20A** is a top perspective view of a multi-dose blister package with a powder release member according to embodiments of the present invention.

**Figure 20B** is a top view of the blister package shown in **Figure 20A** with a plurality of blisters shown having openings formed into their tops according to embodiments of the present invention.

**Figure 20C** is a bottom view of the blister package shown in **Figure 20A** according to embodiments of the present invention.

**Figure 20D** is an enlarged partial side perspective view of the blister package shown in **Figure 20A** with a powder release member positioned to open a top portion of the blister according to embodiments of the present invention.

**Figure 20E** is a perspective top view of the blister package and puncture member shown in **Figure 20D** with the top or overlay of the blister removed except for the opened blisters which illustrate a release (such as a puncture or slit) location according to embodiments of the present invention.

**Figures 21A-21E** illustrate one embodiment of a customized signal generation algorithm for determining a non-linear input signal comprising a plurality of superimposed frequencies according to embodiments of the present invention.

**Figure 22** is a block diagram of a data processing system according to embodiments of the present invention.

Description of Embodiments of the Invention

The present invention will now be described more fully hereinafter with reference to the accompanying figures, in which embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein. Like numbers refer to like elements throughout. In the figures, certain layers, components or features may be exaggerated for clarity, and broken lines illustrate optional features or operations unless specified otherwise. In addition, the sequence of operations (or steps) is not limited to the order presented in the claims unless specifically indicated otherwise. Where used, the terms "attached", "connected", "contacting", and the like, can mean either directly or indirectly, unless stated otherwise.

In the description of the present invention that follows, certain terms are employed to refer to the positional relationship of certain structures relative to other structures. As used herein, the term "front" or "forward" and derivatives thereof refer to the general or primary direction that the dry powder travels as it is dispensed to a patient from a dry powder inhaler; this term is intended to be synonymous with the term "downstream," which is often used in manufacturing or material flow environments to indicate that certain material traveling or being acted upon is farther

along in that process than other material. Conversely, the terms "rearward" and "upstream" and derivatives thereof refer to the directions opposite, respectively, the forward and downstream directions. The term "blister" means a dry powder receptacle that can hold a (typically meted) quantity of a dry powder product. The blister may be configured with an elongated channel or cavity as will be described further below, or configured in other suitable geometries. In operation, the blisters are opened (slit, punctured or otherwise parted) before the dry powder dose is released by the inhaler in the aerosolized inhalant form.

The devices and methods of the present invention may be particularly suitable to dispense dry powder substances to *in vivo* subjects, including animal and, typically, human subjects. The dry powder substance may include one or more active pharmaceutical constituents as well as biocompatible additives that form the desired formulation or blend. As used herein, the term "dry powder" is used interchangeably with "dry powder formulation" and means the dry powder can comprise one or a plurality of constituents or ingredients with one or a plurality of (average) particulate size ranges. The term "low-density" dry powder means dry powders having a density of about 0.8 g/cm$^3$ or less. In particular embodiments, the low-density powder may have a density of about 0.5 g/ cm$^3$ or less. The dry powder may be a dry powder with cohesive or agglomeration tendencies.

In any event, individual dispensable quantities of dry powder formulations can be a single ingredient or a plurality of ingredients, whether active or inactive. The inactive ingredients can include additives added to enhance flowability or to facilitate aeorolization delivery to the desired systemic target. The dry powder drug formulations can include active particulate sizes that vary. The device may be particularly suitable for dry powder formulations having particulates which are in the range of between about 0.5-50μm, typically in the range of between about 0.5μm - 20.0μm, and more typically in the range of between about 0.5μm -8.0μm. The dry powder formulation can also include flow-enhancing ingredients, which typically have particulate sizes that may be larger than the active ingredient particulate sizes. In certain embodiments, the flow-enhancing ingredients can include excipients having particulate sizes on the order of about 50-100 μm. Examples of excipients include lactose and trehalose. Other types of excipients can also be employed, such as, but

not limited to, sugars which are approved by the United States Food and Drug Administration ("FDA") as cryoprotectants (*e.g.*, mannitol) or as solubility enhancers (*e.g.*, cyclodextrine) or other generally recognized as safe ("GRAS") excipients.

Examples of diseases, conditions or disorders that may be treated with the inventive devices and methods include, but are not limited to, asthma, COPD (chronic obstructive pulmonary disease), viral or bacterial infections, influenza, allergies, and other respiratory ailments as well as diabetes and other related insulin resistance disorders. The dry powder inhalant administration may be used to deliver locally acting agents such as antimicrobials, protease inhibitors, and nucleic acids/oligionucleotides as well as systemic agents such as peptides like leuprolide and proteins such as insulin. For example, inhaler-based delivery of antimicrobial agents such as antitubercular compounds, proteins such as insulin for diabetes therapy or other insulin-resistance related disorders, peptides such as leuprolide acetate for treatment of prostate cancer and/or endometriosis and nucleic acids or ogligonucleotides for cystic fibrosis gene therapy may be performed. *See e.g.* Wolff et al., *Generation of Aerosolized Drugs*, J. Aerosol. Med. pp. 89-106 (1994). *See also* U.S. Patent Application Publication No. 20010053761, entitled *Method for Administering ASPB28-Human Insulin* and U.S. Patent Application Publication No. 20010007853, entitled *Method for Administering Monomeric Insulin Analogs*, the contents of which are hereby incorporated by reference as if recited in full herein.

Typical dose amounts of the unitized dry powder mixture dispersed in the inhaler will vary depending on the patient size, the systemic target, and the particular drug. Conventional exemplary dry powder dose amount for an average adult is about 10-30 mg and for an average adolescent pediatric subject is from about 5-10 mg. Exemplary dry powder drugs include, but are not limited to albuterol, fluticasone, beclamethasone, cromolyn, terbutaline, fenoterol, ß-agonists, salmeterol, formoterol, and glucocorticoids. In certain embodiments, the administered bolus or dose can be formulated with an increase in concentration (an increased percentage of active constituents) over conventional blends. Further, the dry powder formulations may be configured as a smaller administerable dose compared to the conventional 10-25 mg doses. For example, each administerable dry powder dose may be on the order of less than about 60-70% of that of conventional doses. In certain particular embodiments, using the active dispersal systems provided by certain embodiments of the DPI

configurations of the instant invention, the adult dose may be reduced to under about 15 mg, such as between about 10μg-10mg, and more typically between about 50μg-10mg. The active constituent(s) concentration may be between about 5-10%. In other embodiments, active constituent concentrations can be in the range of between about 10-20%, 20-25%, or even larger. In particular embodiments, such as for nasal inhalation, target dose amounts may be between about 12-100μg.

In certain particular embodiments, during dose dispensing, the dry powder in a particular dose receptacle may be formulated as only an active pharmaceutical constituent(s), substantially without additives (such as excipients). As used herein, "substantially without additives" means that the dry powder is in a substantially pure active formulation with only minimal amounts of other non-biopharmacological active ingredients. The term "minimal amounts" means that the non-active ingredients may be present, but are present in greatly reduced amounts, relative to the active ingredient(s), such that they comprise less than about 10%, and preferably less than about 5%, of the dispensed dry powder formulation, and, in certain embodiments, the non-active ingredients are present in only trace amounts.

In certain embodiments, the active elements are integral to/included as part of the disposable drug package, unlike many conventional active dispersion systems, cleansing of the active mechanism portion of the inhaler may not be required.

Referring to **Figure 1**, one embodiment of a dry powder inhaler **10** is shown. The inhaler **10** can be configured as an elongated body **10b** defining an internal cavity **10c** (**Figure 8**). The inhaler **10** includes a top primary surface **11** and an opposing bottom primary surface **12** (**Figure 6**). A window **17** may be formed into the body of the inhaler **10** to allow a user to have visual contact with an enclosed multi-dose dry powder package **100**. The window **17** may include a transparent or translucent member or an aperture. The former may reduce environmental contamination during use.

As illustrated, the inhaler **10** can include a pivotably attached cover member **15** that overlies a major portion of the top surface **11**. The cover member **15** can pivot about any desired portion of the device. As shown, the cover member **15** includes an end portion with an aperture **15o** that may correspond to the size of a window **17**. The cover member **15** attaches to the top portion of the elongated body **10b** and pivots

about an axis that is normal to the window **17**. **Figure 1** illustrates the cover member **15** in a closed position where it blends with profile contour of the perimeter of the elongated body **10b**. The cover member **15** may be formed of an elastomeric material that has increased flexibility relative to the elongated body.

As shown in **Figures 3** and **5**, the elongated body **10b** can have a thin profile when viewed from the side with planar top and bottom surfaces **11**, **12**. As used herein, the term "thin" means less than about 1.5 inches thick, and more preferably is about 1 inch or less in width (the width "W" being the distance between the top and bottom surfaces **11**, **12**, as shown in **Figure 5**).

The elongated body **10b** can be configured to be pocket-sized (fitting into standard pockets on male and/or female clothing). By using substantially planar primary surfaces **11**, **12**, and/or a thin profile, the device **10** may be less obtrusively worn (less conspicuous) and/or more conformal to the body and less intrusive in clothing pockets. In certain embodiments, the length of the elongated body is between about 2-5 inches, typically under about 4.25 inches, with the width being about 2-4 inches, typically about 2.5 inches.

**Figure 1** also illustrates that the multi-dose dry powder drug package **100** can include a plurality of circumferentially spaced-apart elongated channels **101**, each sealed with a quantity of dry powder product disposed therein. Each of the elongated channels **101** can be numbered with an alphanumeric indicia **101i** to indicate the present dose located in the dispensing channel. **Figure 7** is an enlarged view of the window and underlying portion of the package **100**. In other embodiments, visible indicia and/or audible alerts can be used to warn a user that he/she is approaching the last of the filled inhalant doses. For example, color enhanced markings can be used for the last few (such as the last 5 doses) the color enhanced may change from darker (orange to salmon or red) or to completely different colors as the last dose or last few doses approach. Alternatively (or additionally), the multi-dose disposable package **100** may be configured with audible alert features that activate a digital signal processor or micro-controller (not shown) housed in the elongated body **10** to generate a stored audible warning (such as "warning, refill needed, only five doses remain) when a desired number of doses have been administered.

Turning to **Figures 2** and **3**, as shown, the cover member **15** can be configured so that a major length is relatively thin and planar and overlies a major

portion of the top surface **11** of the body when the cover member **15** is in a closed position. The outer end portion **15a** of the cover member **15** that covers the mouthpiece **20** can be arcuately configured so as to snugly abut or frictionally align and engage the bottom end portion of the elongated body **10b** when closed. That is, the curvature conforms to the curvature of the bottom or side edge of the elongated body **10e** adjacent the mouthpiece **20**.

**Figure 4** illustrates that the lower portion **15a** of the cover member **15** moves away from the bottom portion **10e** of the elongated body **10b** to reveal the inhalation port **18** of the mouthpiece **20**. This allows a user access to the mouthpiece **20** and associated inhalation port **18**. Because the cover member **15** is retained on the device during normal operation (whether open or closed) and positioned in a non-interfering location, it is less likely to be lost or removed from the device. As shown, the cover member **15** may pivot to reside about the opposing end portion **10oe** and overhang the elongated body **10b**. As the cover member **15** pivots or rotates about the front surface **11**, it exposes an activation button **25** that, when depressed, initiates the active dispensing of the dry powder substance(s) located in the inhalation output or dispensing region of the device **10**. As with conventional inhalant devices, the active inhalation may involve puncturing or disrupting a thin cover material (that may be an elastomeric or polymer sealant cover or even another layer of piezoelectric polymer) disposed over the powder. In any event, the cover member **15** may be configured with an upwardly extending projection region or mound **15p** that is configured to overlie the activation button **25** when closed. The mound **15p** may be configured to define a sufficient air pocket to inhibit inadvertent activation of the button **25**. The mound **15p** may be formed of the same flexible elastomeric material as the remainder of the cover member **15**, or may be formed of a stiffer material for additional protection.

In certain embodiments, the elongated body **10b** may include a recess positioned about the mouthpiece **20** that can be sized to matably receive the cover member **15** therein so that the cover member **15** pops into or nests in and/or locks into the closed position (not shown). Similarly, the pivotal attachment of the cover member **15** can be configured with a ratcheting wheel or gear that biases the cover member **15** into a desired closed and/or open position.

Although shown as positioned to overlie the top surface **11** of the elongated body **10b**, the cover member **15** may be configured to extend from the bottom surface **12** upwardly to cover the mouthpiece **20**. Similarly, the pivotal attachment can be laterally offset instead of longitudinally offset as shown.

**Figure 6** illustrates that the bottom surface **12** of the elongated body **10b** can include an indexing mechanism **30** that allows a user to advance the multi-dose package **100** to the next dry powder dose. The indexing mechanism **30** or a similar knob can include alignment indicia **30i** (shown herein as an arrowhead) that can be aligned with alignment indicia **10i** on the housing body **10b** to allow the elongated body **10b** to be disassembled and more easily reassembled with a replacement disposable multidose package **100**. The indexing mechanism **30** can reside in other locations and configured in other electrical and/or mechanical configurations.

In certain embodiments, the mouthpiece **20** can be removed by disengaging and/or pulling it from its adjacent portion of the inhaler **10** without requiring further disassembly of other components. This can allow the mouthpiece **20** to be cleaned as desired. Typically, the mouthpiece **20** is snapped into and held in position by a friction fit joint. Of course, other connection components and configurations may also be used as is known to those of skill in the art.

**Figure 8** illustrates that the elongated body **10b** can be configured as two primary matable first and second housing members **11b**, **12b** that allow the disposable package **100** to be replaced as needed. In other embodiments, the entire elongated body **10b** and contents are disposable after depletion of the dispensable doses (whether a 30, 60, 90 or other day supply). The contents typically include the control system, a microchip such as a digital signal processor (not shown), power source (battery)(not shown), and the package **100**.

**Figure 8** illustrates the package **100** in the cavity **10c** with the elongated channels **101** formed of the piezoelectric polymer material oriented with the projection curving up (projecting upwardly). In this embodiment, the piezoelectric material can define the ceiling and the opposing sidewalls. However, in certain embodiments, as shown in **Figures 9**, **10A**, and **10B** the package **100** has a reversed orientation so that the elongated channels **101** have the projection curving down (projecting downwardly). In the latter configuration, the piezoelectric material can define the floor and sidewalls of the channel **101**. As will be described further below,

the piezoelectric polymer material can be deposited, coated, sprayed, inked, foiled, or otherwise layered with a metallic conductive material at selected regions of the package **100** and along at least a portion of each of the elongated channels **101** to define a vibrating or flexing active region when activated by an excitation voltage.

**Figure 9** illustrates that the elongated channels may include a sealant layer **120** that seals the elongated channels **101**. The sealant layer **120** may be a thin polymer film material, a foil layer, and, in certain embodiments, may be another layer of piezoelectric polymer film that is also coated or layered with metal to become activated during dispensing. In any event, the sealant layer **120** may be a ceiling with an end portion **120s** that is scored, notched or otherwise formed so that it is preferentially predisposed to part, puncture or split upon exposure to a blunt pressure (such as based on actual contact with a dose release or puncture device or an elevated pressure). In certain embodiments, the end portion **120s** closest to the mouth of the user is notched or scored to increase the travel distance of the dry powder along the length of the elongated channel **101**, which can increase the interchange between the dry powder and the piezoelectric material; this can increase the amount of energy transferred to the dry powder from the oscillating or vibrating active piezoelectric polymer film so as to cause the dry powder to vibrate at a frequency that is at or near a resonant frequency thereof.

In certain embodiments, the elongated channels **101** can be shaped and/or sized to define a resonant chamber or cavity to generate a desired frequency(ies) of oscillation of the piezoelectric polymer material and/or a particular dry powder formulation. That is, each blend or formulation of dry powder may exhibit different flow characteristics that can be accounted for in the geometry design of the elongated channel **101**. The height or depth, length, or width of the channel may be adjusted based on the particular drug or dry powder being administered. Advantageously, the inhaler **10** can be configured to dispense a number of different dry powder packages **100**, each having the potential of having different drug receptacle or blister configurations. For example, the package **100** may be fabricated with 2-10 different standard lengths and a particular drug or formulation and dose matched to one of the predetermined standard lengths based on the closest match to generate an optimum vibration frequency. In other embodiments, the length of the channel and/or other parameters can be custom designed and defined for each formulation or drug that is to

be administered using the inhaler device **10** and the inhaler device **10** can be configured to operate with and/or accommodate each custom package **100**.

**Figure 16A** illustrates an example of an amplitude-modified vibratory signal **20s** (**Figure 10A**) of a dry powder that can include a kHz carrier frequency (such as about 5kHz-50kHz) modified by low modulating frequency (typically about 10-200Hz) that may be generated and used to dispense a dose of dry powder from a blister channel **101** (**Figure 10A**) as contemplated by certain embodiments of the present invention. The frequency of the vibration can be modified to match or correspond to the flow characteristics of the dry powder substance held in the package to attempt to reach a resonant frequency(s) to promote uniform drug dispersion into the body. In certain embodiments, the vibration of the active piezoelectric surfaces in the channel **101** may be on the order of about 10-200 Hz. In certain embodiments, the frequency may be between at about 10-60Hz. The vibration can be influenced by the amount of active surface and the excitation voltage pulses applied thereto as well as the channel geometry. During dispensing, a channel **101** can be activated by providing a voltage across the piezoelectric layer. In certain embodiments, the voltage provided may be at about 100-400 volts peak-to-peak, typically between about 200-400 volts peak-to-peak. In other embodiments, the voltage can be applied at a different level and at other various frequencies, such as at higher frequencies of between about 25kHz to about 2MHz. Additional suitable excitation signals will be discussed further below.

In certain embodiments, the signal **20s** (shown schematically in **Figures 10A, 10B** with respect to the channel **101**) and/or the vibration of the energy provided to the channel **101** may be configured to concurrently or successively rapidly vibrate the dry powder at a plurality of different frequencies (at similar or different amplitudes) in the range of between about 10 Hz-1000 kHz. In certain embodiments, the frequencies are between about 10-200 Hz, such as 10-60 Hz. In other embodiments, they may be in the range of between about 7kHz-100 kHz, such as 7.5kHz or more such as frequencies between about 15 kHz to 50 kHz.

In particular embodiments, as schematically shown in **Figures 16B-16D**, a non-linear powder-specific dry powder vibratory energy signal **20s** (shown as a different powder specific signal for each of the simulated illustrated formulations shown as "A", "B" and "C") comprising a plurality of selected frequencies can be

generated (corresponding to the particular dry powder being currently dispensed) to output the particular signal corresponding to the dry powder then being dispensed. As used herein, the term "non-linear" means that the vibratory action or signal applied to the package to deliver a dose of dry powder to a user has an irregular shape or cycle, typically employing multiple superimposed frequencies, and/or a vibratory frequency line shape that has varying amplitudes (peaks) and peak widths over typical standard intervals (per second, minute, etc.) over time. In contrast to conventional systems, the non-linear vibratory signal input can operate without a fixed single or steady state repeating amplitude at a fixed frequency or cycle. This non-linear vibratory input can be applied to the blister to generate a variable amplitude motion (in either a one, two and/or three-dimensional vibratory motion). The non-linear signal fluidizes the powder in such a way that a powder "flow resonance" is generated allowing active flowable dispensing.

**Figures 16B-16D** illustrate three different dry powders **$215_1$, $215_2$, $215_3$**, each of which can be analyzed and/or characterized (**$20ch_1$, $20ch_2$, $20ch_3$**, respectively). Custom or corresponding individual (non-linear) input signals with frequencies selected from the corresponding characterization that are specifically targeted to that dry powder to facilitate fluidic flow during dispensing can be determined for each dry powder **$215_1$, $215_2$, $215_3$**. The drug-specific signals are shown by the signals **$20s_1$-$20s_3$**.

The inhalers **10** include signal generating circuitry **10g** therein in communication with the channels **101**. The signal generating circuitry **20g** may be programmed with a plurality of predetermined different signals **20s**, or if the inhaler dispenses only a single dry powder, the signal generator **20** may be programmed with a single signal **20s**. Appropriate powder-specific signals can be determined experimentally and/or computationally at an OEM or evaluation site and input into the inhalers (via hardware and/or software components including programmable processors).

**Figures 21A-12E** illustrate an example of operations that may be carried out to generate a dry powder-specific signal. A microflow analysis of the dry powder to be dispensed can be performed to assess avalanching flow profiles and/or other suitable mass/time flow profiles. The analysis can be carried out to select predominant oscillatory frequencies for a particular dry powder that, when applied to

the powder during flowable dispensing, can promote uniform mass flow to achieve a fluid-like flow, even for low-density dry powders.

Methods and devices for analyzing rapid powder flow measurement are described in Crowder et al., *Signal Processing and Analysis Applied to Powder Behavior in a Rotating Drum,* Part. Part. Syst, Charact. 16, 191-196 (1999); Crowder et al, *An instrument for rapid powder flow measurement and temporal fractal analysis*, Part Syst Charact 16, pp. 32-34, (1999); and Morales-Gamboa, et al., *Two dimensional avalanches as stochastic Markov processes*, Phys Rev. E, 47 R2229-2232 (1993), the contents of which are hereby incorporated by reference as if recited in full herein. *See also*, Ditto et al., *Experimental control of chaos*, Phys. Rev. Lett., 65: 3211-3214 (1990); B. H. Kaye, *Characterizing the Flow of Metal and Ceramic Powders Using the Concepts of Fractal Geometry and Chaos Theory to Interpret the Avalanching Behaviour of a Powder,* in T.P. Battle, H. Henein (eds.), *Processing and Handling of Powders and Dusts, The Materials and Metals Society*, 1997; B. H. Kaye, J. Gratton-Liimatainen, and N. Faddis. *Studying the Avalanching Behaviour of a Powder in a Rotating Disc.*, Part. Part. Syst. Charact. 12:232-236 (1995), and Ott et al., *Controlling Chaos*, Phys. Rev. Lett. 64: 1196-1199 (1990), the contents of each of these articles are also incorporated by reference as if recited in full herein. Using the principals and relationships described in one or more of these articles with signals derived from analyses of mass flow and/or microflow, one can determine custom powder specific signals that may be able to achieve uniformly flowing dry powders.

As shown in **Figure 21A**, the time between avalanches, for a particular dry powder of interest, may be evaluated experimentally using a rotating drum. This time information may be converted to frequency space (frequency domain) as shown in **Figure 21B**. **Figure 21C** illustrates that a distribution of frequencies **20f** can be determined (computationally or via computer models). Then, a desired number of selected frequencies can be identified. The frequencies selected may span a desired statistically significant percentage of the distribution or be the frequencies most observed in the analysis spectrum. The term "most observed" means those frequencies occurring the greatest number of times in the distribution. For example, the number of different frequencies selected may be at least the three most observed different frequencies and/or sufficient frequencies to represent at least about 50% of the distribution. In certain embodiments, the number can be at least about 5, and

typically about 6, or a number sufficient to represent at least about 75% of the frequency distribution. To select the number, two or three of the most observed frequencies can be used to form the vibration signal. The results can be analyzed experimentally and additional frequencies may be added to the combined non-linear signal to improve fluidic flow performance.

**Figure 21D** illustrates that six of the most observed frequencies **$20f_1$-$20f_6$**, in the distribution plot **20f** can be selected. **Figure 21E** illustrates that the selected frequencies can be superimposed to generate a single superposition signal (that may also include weighted amplitudes for certain of the selected frequencies or adjustments of relative amplitudes according to the observed frequency distribution). Thus, **Figure 21E** illustrates a derived non-linear oscillatory or vibratory energy signal that may be used to dispense a particular dry powder.

Referring again to **Figure 21D**, the signal can be created digitally by computer code means employing mathematical or numerical computation techniques and relevant equations. For example, for a signal **20s** having representative frequencies "$f_{1\text{-}n}$," the cumulative signal $x_{signal}$ **(20s, Figure 21D)** can be generated include a plurality of signal components, $xf_1$-$xf_n$ (shown as **$20f_1$-$20f_n$ in Figure 21D**) at each desired frequency, $f_n$, each component having an amplitude "a" at its frequency as described below. Using the spectrum shown in **Figure 21D** noting that the most observed frequency in **Figure 21D** is **$20f_3$**, the following equations may be used to generate the non-linear signal.

For an index, "n" ranging from 0-15,999, used to generate the digital signal:

$n = [0:15999]$ Equation (1)

$xf_3 = \sin(2\pi n/16000)$ Equation (2)

$xf_2 = af_2 \sin(2\pi n (f_2)/16000(f_3))$ Equation (3)

$xf_4 = af_4 \sin(2\pi n (f_4)/16000(f_3))$ Equation (4)

This evaluation can be continued for a desired number of frequencies to render a representation of a sufficient number of frequencies /spanning a sufficient portion of the spectrum. The powder-specific, non-linear signal can be generated by summing the selected individual frequency components.

$$x_{signal} = xf_3 + xf_4 + xf_4 \ldots \quad \text{Equation (5)}$$

In certain embodiments, the overall power in the signal, $x_{signal}$, can be increased by adding a phase shift to one or more of the summed components. For example, for component $xf_2$, the associated signal contribution can be adjusted by the following equation:

$$xf_2 = af_2 \sin(2\pi n (f_2)/16000(f_3) + m\pi/n_f) \quad \text{Equation (6)}$$

Where "m" is the number at this frequency and $n_f$ is the total number of frequencies contained in the signal.

An example of a commercially available rotating drum is the TSI Amherst Aero-Flow™ (TSI Inc. Particle Instruments/Amherst, Amherst, MA). This device provides powder flow information by detecting the occurrence of and recording the time between avalanches. The Aero-Flow™ has been utilized to demonstrate correlation between powder flow and tableting performance for like materials. The instrument uses a photocell detector for its avalanche detection mechanism. A light shines through the plexiglas drum and is obscured from the detector to varying degrees by powder contained in the drum. As the drum rotates, the powder heap rises with the rotation and the photocell detector is uncovered. When an avalanche occurs in the powder heap, the light is again blocked by the cascading powder. The change in light intensity striking the photocell is interpreted by the data collection software as the occurrence of an avalanche. In other embodiments, the occurrence of avalanches can be measured using a sensitive microphone/accelerometer that can be mounted on the rotating drum. Avalanches can be detected acoustically from the sound generated by the avalanching powder. This technique can reduce the amount of powder used, typically to milligram quantities, such as about 10 mg. Statistics of the time between avalanches are determined and an avalanche time phase space plot is generated.

A useful method of presenting data to discover the dynamics of a system is the Poincaré phase space plot. This phase space approach is one in which variables sufficient to describe a system are contained in a single vector. The state of the *n* variables at an instant in time is a point in phase space. Plotting the time evolution of the system in phase space can map its dynamics. As an example, a simple harmonic

oscillator can be pictured in phase space by plotting the position versus the velocity, variables that completely describe the system. The phase space plot of the harmonic oscillator is a circle reflecting the periodic, but 90 degrees out of phase, exchange of maximum position and velocity. A damped harmonic oscillator would appear as a simple attractor with the trajectory encircling and eventually collapsing to the origin as the position and velocity reach zero. The correlation dimension provides a measure of the space filling properties of the phase space representation. A hypersphere of dimension D and radius r is centered on each data point. The number of data points falling within that sphere as a function of the radius may be displayed in a log-log plot. The slope of the resulting line may be termed the correlation dimension.

To determine an appropriate vibration signal, a suitably sized dry powder sample can be disposed in the drum (such as about 60 ml or less of powder as noted above). The drum can be allowed to rotate through a single revolution before data collection begins so that initial conditions over several powders are similar. The drum can be rotated at 0.5 revolutions per minute for 6 minutes. The photocell voltage signal can be sampled at 25 Hz using a PC based data acquisition board (DI-170, Dataq Instruments, Akron OH). Time between avalanches and the voltage change upon avalanching can be acquired from the voltage signal. A video camera can be situated perpendicular to the drum can record the powder as it rotates in the drum. A grid can be placed behind the drum, without obscuring the photocell, to facilitate determination of the angle of the powder relative to the horizontal. Upon viewing the video, the base and height of the powder heap can be recorded and the angle can be determined using the trigonometric relation, $\theta = \arctan(\text{height/base})$. Determinations of the instantaneous powder angle can be performed at 200 millisecond intervals. This rate corresponds to every sixth frame of the video, determined previously by recording the counting of a stopwatch.

Angle data time series can comprise at least about 500 data points or 100 seconds. Computation of a Fourier power spectrum can be performed using the Welch method with a 128 point Kaiser window and zero padding to 1024 data points for the FFT calculation. Other suitable methods can be employed as is known to those of skill in the art.

The avalanche statistics can be presented in terms of the mean and standard deviation of time between avalanches. A phase space plot can be generated by

plotting the $n^{th}$ time to avalanche against the $(n-1)^{th}$ time to avalanche. For the angle of repose, phase space plots consist of the instantaneous deviation from the mean angle versus the first time derivative of the angle. The rate of change of the angle at each data point can be approximated from the preceding and subsequent data points using Newton's method.

The uniformity of flow can be discerned by examining the frequency and the amplitude of the oscillations. Certain dry powder signals may exhibit a higher degree of variability in frequency and in amplitude relative to others. By use of the Fourier transform (FT) power spectrum, energy distributions can be obtained. Energy spectrums that are dispersed over a range of frequencies can indicate more irregular flow. The mean time to avalanche can be subtracted from the instantaneous time to avalanche to deconvolute relevant frequency data in angle phase space plots. Identifying the predominant frequencies and selectively combining and/or using those identified frequencies as the basis of the transmitted vibration energy excitation signal may induce resonance in the dry powder during dispensing.

Alternatively, the non-linear signal can be determined experimentally as described in co-assigned, co-pending U.S. Patent Application Serial No. 60/440,513, the contents of which was incorporated by reference hereinabove. Generally described, a flow channel housing having an angularly adjustable elongate flow channel therein can be used to determine appropriate powder-specific signals. A dry powder of interest (which may be a low density dry powder) can be introduced into the elongate flow channel. The flow channel can be vibrated to thereby vibrate the dry powder to cause the dry powder to fluidly flow out of the channel via an exit port. The flow channel can include a flexible piezoelectric polymer over which the dry powder flows; the piezoelectric polymer can be electrically stimulated to flex upwardly to cause it to vibrate the powder as the powder travels along and through the flow channel. As described above, the vibration can carried out using a non-linear excitation signal having a carrier frequency and a modulation frequency. In certain embodiments, the carrier frequency can be between about 2.5kHz-50kHz and modulation frequency may be between about 10-500Hz. In any event, flow characteristics can be experimentally evaluated, typically over several different input signals at different frequencies, and at least one frequency (and/or angular orientation of the flow path) selected for its ability to generate reproducible fluidic flow of dry

powder based on the flow characteristics exhibited during the vibrating step. The orientation of the flow channel can be adjusted so that the flow channel is angularly offset (with the dispensing port located lower than the input port) in the axial direction with respect to the horizontal and vertical axis. In certain embodiments, the flow channel is adjusted to be at different selected angles during the evaluation to consider the impact that the angle may have on the dispensing flow.

In any event, in certain embodiments, the output signals **20s** used to activate the piezoelectric channels **101** may be include a plurality, typically at least three, superpositioned modulating frequencies and a selected carrier frequency. The modulating frequencies can be in the range noted herein (typically between about 10-500 Hz), and, in certain embodiments may include at least three, and typically about four superpositioned modulating frequencies in the range of between about 10-100Hz, and more typically, four superpositioned modulating frequencies in the range of between about 10-15Hz.

**Figure 10A** illustrates one embodiment of an elongate channel **101**. The channel **101** has a length that is greater than its width. In certain embodiments, the length may be at least twice the distance of the width. As shown, the elongate channel **101** includes a ceiling **120** and a floor **100f**. The floor **100f** includes a metallic material layer **100m** thereon. The ceiling **120** can be configured to be preferentially pre-disposed to separate at a desired location **120s** as noted above. Referring to **Figure 9**, the metallic region **100m** on the channel **101** is in communication with a metal trace **100t** that extends a distance away from the channel **101** and, in operation, can engage a power source and relay the input signal from the signal generator circuitry **20g**.

Increased numbers of doses may be held on a single disposable package **100**, whether symmetrically aligned or offset one to another on a single primary surface, or formed on opposing primary surfaces (the package can be flipped to access the underside portion of doses). In certain embodiments, about 50-100 discrete doses or more can be held on the package **100** (not shown).

**Figure 10B** illustrates that the channel **101** can be configured so that the floor 100f slopes or descends a distance over the length of the channel **101** so that the downstream end of the channel **101** during dispensing and/or the region more proximate the preferentially predisposed separation portion has a greater depth. This

can allow gravity to help move the powder along the length of the channel **101,** allowing the dry powder to contact a greater active amount of active or vibrating piezoelectric polymer surface area. As such, the elongated channels **101** contemplated by embodiments of the present invention may amplify the vibration frequency of the dry powder before it is released to the user. In yet other embodiments, the cavity of the channel can narrow and/or become more shallow as it approaches the end portion that is proximate the mouth of the user during dispensing (**Figure 17A**).

**Figure 11** illustrates another embodiment of the present invention. In this embodiment, a sensor that can detect one or more patient-air flow related parameters *in situ* during each dispensing, can be incorporated directly into the disposable multi-dose packaging **100**. As shown, each blister **101'** or channel **101** (**Figure 1**) can have a proximately positioned airflow parameter sensor circuit **150**. The circuit **150** includes conductive traces **150t** and a sensor **150s** that can detect air pressure differential or airflow rate. If the sensor **150s** detects air pressure differential, this can be compared to predetermined airflow rate information, such as *a priori* knowledge of the inhaler's airflow resistance to determine inspiratory capacity of the user. This data can be analyzed in the controller and the energy applied to the blister or channel adjusted. In certain embodiments, the sensor **150s** can be a hot-wire anemometer that is mounted to the package **100** so that it is in fluid communication with the user during operation and powered via the metallic traces **150t** when connected to the power source. In other embodiments the piezoelectric polymer layer **28** can define a pressure sensor that detects pressure differential based on its flexure and relay the signal to the controller (not shown).

**Figures 12A** and **12B** illustrates that a plurality of individual multi-dose packages **100a**, **100b** can be stacked in a tier configuration. In the embodiment shown, two packages are stacked, but three, four, or more may also be stacked according to embodiments of the present invention. The dry powder filled blisters **101** can be oriented so as to be in the same or opposing directions package-to-package. In the embodiment shown in **Figure 12B**, the blisters are channels **101** and are disposed in package **100a** with the arcuately curved portion **101a** oriented downward while the lower package **100b** is held with the arcuately curved portion **101a** oriented upward. The orientations of the channels can be reversed or placed to

both face up or down or even alternated on each particular package **100a**, **100b** (not shown). The packages **100a**, **100b** can include the same or different channel layout and/or can be angularly offset about an axis extending normal to the packages **100a**, **100b** and through the centers thereof, when positioned in the inhaler **10**. For example, the top package **100a** may be rotated so that the underlying channels are misaligned by 5, 30, 45, 60, 90, or 120 degrees or more. Further, a plurality of discrete channels **101** can be provided so that they are aligned end to end in a radially spaced apart configuration (**Figure 12C**).

In certain embodiments, each package, or blisters **101** on a particular package **100,** may be filled with the same dry powder products, while in other embodiments, each package may be filled with different formulations of dry product (and may have different blister geometry). In certain particular embodiments, the inhaler **10** can be configured so that the packages **100** can provide a combination therapy of two or more different drugs that can be administered concurrently or separately to a subject.

As shown by the two-way arrows in **Figures 12A** and **12B**, the stacked tier package configuration can be spring loaded in the inhaler **10** so that the two packages **100a**, **100b** can be compressed toward each other at activation and the powder in a channel on the top package **100a** can be concurrently released with the powder in a corresponding channel on the bottom package **100b**. The packages **100a**, **100b** can then be released to move away from each other decompressing the spring during non-active dispensing.

**Figure 13** illustrates a thin strip package **100s** with a plurality of elongated channels **101** positioned along its length. The strip package **100s** may be scrolled along two tension rods **200a**, **200b** as shown to position the dispensing portion in the desired location in the inhaler (advancing the used empty blisters similar to a camera film cartridge). In certain embodiments, as shown in **Figure 13**, two side-by-side scrolled strips **100s**, **100s** can be employed. This side-by-side arrangement may be particularly suitable for combination therapies or deliveries as described above. In other embodiments, the scrolled strips **100s** may be placed in a stacked tier one above the other (not shown).

**Figures 14A** and **14B** illustrate yet another embodiment of a blister package arrangement. As shown, the package **100sp** is vertically undulated and/or spiraled. The adjacent tiers can be coaxially aligned or adjacent tiers or levels can be disposed

off center or horizontally offset from the others. The tiers can be arranged in a serpentine arrangement from top to bottom (or side-to-side if oriented laterally instead of longitudinally as shown) to provide spaced apart dry powder blisters channels **101** in spaced apart tiers. The spiral or serpentine arrangement can be provided by arranging a plurality of discrete packages in the desired configuration, by configuring one or more strips or sheets in a spiral configuration and/or by folding a single sheet or strip over on itself to take on a serpentine shape.

**Figures 15A-15C** illustrate an additional embodiment of an inhaler **10'**. As shown, the body of the inhaler **10'** has a hinge **10h** along one edge portion connecting two housing members **11a, 12b** and allowing access to the interior cavity **10c**. The top housing member **11a** holds the mouthpiece **20** and associated inhalation port **18**. The bottom member **12b** can hold the electronics module **40** (**Figure 15B**). As described above, the inhaler **10'** houses the dry powder blister package **100**. The top housing member **11a** may include a spring-loaded connector **13** that facilitates a snug connection between the housing members **11a, 12b,** mouthpiece and package **100** when closed and can also provide a conductive connection **13c** to the top surface of the blister traces **100t**. As shown, the mouthpiece **20** can include an aperture **20a** that will overlie a blister region **101** on the package **100** when the inhaler **10'** is closed. As shown in **Figure 15A**, the package **100** can include a central air aperture **102** that allows air to travel in the cavity **10c**. The mouthpiece **20** can be configured to rotate (noted by the arrow in **Figure 15A**) about the top housing member **11b** so that it can serially overlie each filled blister for inhalation.

The package **100** can include a tab **100t** (shown as a notch or cut-out region along the perimeter of the package) that fits into the housing in a desired location to facilitate proper loading in the housing **12b**. **Figure 15B** illustrates the closed shape and **Figure 15C** illustrates the blister package **100**.

**Figures 17A** and **17B** illustrate another embodiment of a blister **100b** with an elongate channel **101**. In this embodiment, the blister **100b** includes both upwardly and downwardly extending portions. The downwardly extending portion **100d** is an elongate lower channel **101** and the upwardly extending portion **100u** is a protrusion that can be substantially arcuate and positioned to reside over a forward portion of the blister **100b** with the upstream ceiling **120** portion being substantially planar over the remainder of the underlying channel **101**.

As shown by the arrow in **Figure 17A**, a dose release member **299** can be disposed in the inhaler **10** so as to approach the blister channel **101** from under the floor **100f** of the package **100**. As shown by the arrow in **Figure 17B**, the release member **299** can then return to its static position to be subsequently actuated again for a next release. The release member **299** can be configured with an end portion **299e** that has a shape or profile that is substantially the same as the top blister portion **100u** of the ceiling **120** overlying the channel **101** in the target release zone. The release member **299** can be configured to puncture, slit, slice, burst, burn, puncture, pierce, melt, or otherwise separate or form the release port or opening in the target region of the floor **101f**.

In the embodiment shown in **Figures 17A** and **17B**, both the upper portion of the release member **299e** and a portion of the ceiling **120** have a substantially upwardly arching or arcuate profile. In certain embodiments, the upper portion **299e** may be semi-spherical. In operation, as shown in **Figure 17B**, the upper portion of the release member **299** advances to contact and invert the lower portion of the blister (*i.e.*, the loose region of the floor **100l**) into the upper blister or ceiling thereby creating a relatively large exit port for the dry powder to exit the channel. The configuration of the release member **299** may reduce the likelihood that the loose end of the floor material will fold back or otherwise impede the release of powder during administration.

In the embodiment shown in **Figures 17A**, **17B** and **18A-18E**, the target opening region **100r** may be a forward portion of the floor **100f**. The floor **100f** can be formed from and/or include the active piezoelectric polymer material (referred to generally as feature **28**) so that, in operation, the floor **100f** can flex in response to the applied signal **20s** to impart the active delivery vibration energy to the dry powder. In other embodiments, the release region **100r** can be formed in a floor that is non-active, such as a foil and/or polymer layer and the ceiling **120** can be formed from the piezoelectric polymer material **28** with the ceiling **120** configured to flex to impart the desired dispersion energy to the dry powder. Combinations of the above may also be employed.

**Figure 18A** illustrates the top of one package **100** configuration that can operate as described for **Figures 17A** and **17B**. **Figures 18B** and **18C** illustrate opposing top and bottom primary surfaces of the package **100** shown in **Figure 18A**.

**Figures 18C** and **18D** illustrate that the elongate channel **101** may have a curvilinear outer profile when viewed from the top that narrows in width from the rear of the channel **101r** to the forward portion of the channel **101fr**. In addition, the rear portion **101r** can have a greater depth (as well as a larger cross-width) than the forward portion **101fr**. As shown, the elongate channel **101** may be configured as a substantially pear-shaped dry powder basin or reservoir. **Figure 18E** is shown without the top blister ceiling **120** and illustrates the release member **299** in position as it forms the opening or release region **100r** in the floor **100f** of the channel **101**. In operation, the ceiling **120** upstream of the blister **100b** can remain intact. The inhaler **10** may be configured with an exit port that is in fluid communication with the package bottom of the blister **100d** (not shown).

**Figures 19A** and **19B** illustrate another embodiment of a blister **100b** with an elongate channel **101** with the release member **299** configured to open the blister **100b** from the ceiling **120** of the package. The arrows in **Figures 19A** and **19B** illustrate the direction of movement relative to the package **100** orientation. As discussed with respect to **Figures 17A, 17B,** and **18A-18E**, in this embodiment, the blister **100b** can include both upwardly and downwardly extending protrusion portions **100u**, **100d**. As before, the downwardly extending portion **100d** can be formed as a depression that defines the elongate (lower) channel **101** and the upwardly extending portion **100u** can be formed as a protrusion that may be substantially arcuate and positioned to reside over a forward portion of the blister **100b** with the upstream ceiling **120** portion being substantially planar over the remainder of the underlying channel **101**. The release member forward portion **299e** can be configured with a profile that corresponds to the shape of the floor **100f** or channel **101** at the lower portion of the blister **100d**. The forward contact portion **299e** may have a profile that is semi-spherical and/or when viewed from the side, it may have a profile that is substantially arcuate or semi-circular. In operation, as shown in **Figure 19B**, the release member **299** can invert the profile of the loose end **100r** created by the opening in the ceiling portion **100u** so that it substantially blends with and/or conforms to the shape of lower blister **100d** as shown in **Figure 19B**. That is, the loose edge portion can extend away from the direction of flow but is configured so that it resides proximate the bottom of the channel **101** so that it does

not impede the dry powder flow out of the channel **101**. The floor **100f** of the channel may include the piezoelectric polymer material **28.**

**Figure 20A** illustrates the release member **299** positioned over the package **100** with a series of blisters **100b** having openings or release zones **100r** that have been (serially) opened by the release member **299**. **Figure 20B** illustrates the top or ceiling side of the package **100** shown in **Figure 20A**. **Figure 20C** illustrates another elongate channel **101** configuration for the floor **100f** that forms the bottom portion of the blister **100d**. As shown in **Figure 19B** and **Figure 20D**, in this embodiment, the elongate channel **101**can have a substantially constant depth along its length. **Figure 20E** shows the channel **101** from the top with the ceiling **120** substantially transparent except about the opening **100r** for clarity.

It is noted that, in operation, depending on how the package **100** and release member **299** are oriented in the inhaler **10,** the release member **299** may approach the package **100** from the top or side so that it engages the package ceiling **120** proximate the blister **100b** (such as shown for the embodiment shown in **Figures 19A** and **19B**) or bottom or opposing side (such as for the embodiment shown in **Figures 17A** and **17B**) so that it engages the package floor **100f** proximate the blister **100b.**

In operation, a priming signal can be applied to the blister **100b** prior to forming the opening in the blister **100b** to vibrate the dry powder held therein to the lowest portion of the elongate flow channel, which can be described as a blister reservoir or basin **101b**. The release member **299** can be directed to open the blister **100b** during or after application of the priming signal. The priming signal may be the same signal as the active delivery signal **20s** or may be a different signal.

The release member **299** may be configured as any suitable device for inserting or forming the opening in the blister **100b**. The release member **299** can be configured to pierce, puncture, slice, melt, or otherwise form the opening in the blister. The release member **299** can include a blade, a laser, pressurized fluid, acoustic energy, or other release or separation means. The release member **299** may be spring loaded to automatically actuate upon a user's depression of a dispensing mechanism.

To facilitate dry powder administration through the inhaler port, the active dispensing signal **20s** can be applied to the vibrating layer substantially instantaneous (*i.e.*, during) with the introduction of the opening **100r** in the blister **100b**. In other

embodiments, the signal **20s** can be applied before the opening **100r** is formed (typically within about 50ms) or shortly after the opening is introduced into the blister (typically within about 50ms).

In certain embodiments, each blister **100b** can have its own operative electrical parameter and associated electrical connections that engage with a central control unit in the inhaler **10** and can be used to verify proper operative alignment. That is, an electronics module with signal generating circuitry **20g** can communicate separately with the electrical traces **100t** proximate each blister region **101** to sense a desired electrical parameter such as capacitance of the piezoelectric polymer blister. In other embodiments, the sensed parameter can be an open connection in the electrical path indicating improper alignment.

In particular embodiments, such as for rotating mouthpiece configurations, the device can be configured with a plurality of predefined stops (recesses, projections, etc...) that allow the mouthpiece **20** to click into position in a manner that yields an audible or tactile verification by the user at each dispensing blister (not shown).

In certain embodiments, the piezoelectric polymer material, shown generally as element **28** in **Figures 9** *et seq.*, and which is included in the blister packages **100** of embodiments of the invention, is formed from a piezoelectrically active material such as PVDF (known as KYNAR piezo film or polyvinylidene fluoride) and its copolymers or polyvinylidene difluoride and its copolymers (such as PVDF with its copolymer trifluoroethylene (PVDF-TrFe)).

In particular embodiments, the piezoelectric polymer material layer **28** is a thin film PVDF. As used herein, the term "thin film" means that the piezoelectric polymer layer **28** is configured as a structurally flexible or pliable layer that can be sized to be about 10-200μm thick. In certain embodiments, the piezoelectric polymer layer can be sized to be less than about 100 μm thick, and more typically, about 20-60 μm thick.

As noted above, selected regions of the piezoelectric polymer material can be coated or layered with a conductive material to form a desired conductive pattern. The conductive regions (at least portions of the blister regions) of the package **100** define the active regions and can be individually or selectively activated during operation. Laminates of PVDF and another material capable of being formed into and hold a desired blister shape and/or powder channel may be particularly suitable

for forming the active blister configurations. Suitable laminates include thin film layers of PVDF united to thin layers of one or more of aluminum, PVC and nylon films. The PVDF may form the bottom, top, or an intermediate layer of the laminated material structure. For intermediate layer configurations, vias and/or edge connections can be used to apply the electric signal to the blister piezoelectric material.

The metal trace patterns can be provided by applying a conductive pattern onto one or more of the outer faces of the piezoelectric substrate layer. For depositing or forming the metal, any metal depositing or layering technique can be employed such as electron beam evaporation, thermal evaporation, painting, spraying, dipping, or sputtering a conductive material or metallic paint and the like or material over the selected surfaces of the piezoelectric substrate (preferably a PVDF layer as noted above). Of course, alternative metallic circuits, foils, surfaces, or techniques can also be employed, such as attaching a conductive mylar layer or flex circuit over the desired portion of the outer surface of the piezoelectric substrate layer **28**. It is preferred that, if flex circuits are used, they are configured or attached to the substrate layer **28** so as to be substantially transparent to the structure of the sensor array to minimize any potential dampening interference with the substrate layer **28**. It is also noted that while particular conductive patterns are illustrated in the figures, the present invention is not limited thereto, as alternative conductive patterns may also be used.

Typically, upper and lower surface metal trace patterns are formed on opposing sides of the piezoelectric polymer material but do not connect or contact each other. For example, conductive paint or ink (such as silver or gold) can be applied onto the major surfaces of the package about the elongated channels and associated metal traces such that it does not extend over the perimeter edge portions **28e** of the piezoelectric substrate layer **28**, thereby keeping the metal trace patterns on the top and bottom surfaces separated with the piezoelectric substrate layer **28** therebetween. This configuration forms the electrical excitation path when connected to a control system to provide the input/excitation signal for creating the electrical field that activates the deformation of the piezoelectric substrate layer **28** during operation. As such, the electrical path for each elongated channel **101** extends via the respective upper and lower transmission lines to the electrical terminations operably

connected to the controller. The excitation circuit (signal generating circuitry **20g**) configuration can be such that the upper trace operates with a positive polarity while the lower trace has a negative polarity or ground, or vice versa (thereby providing the electric field/ voltage differential to excite the piezoelectric substrate in the region of the selected channel **101**). Of course, the polarities can also be rapidly reversed during application of the excitation signal (such as + to -, or + to -) depending on the type of excitation signal used, thereby flexing the piezoelectric material in the region of the receptacle portion. For a more complete discussion of the active excitation path or configuration, *see* U.S. Provisional Application Serial No. 60/188,543 to Hickey et al., incorporated by reference hereinabove.

In certain embodiments, methods for fabricating a multi-dose disposable dry powder blister package include: (a) providing a thin layer of piezoelectric polymer material; (b) concurrently forming a plurality of elongated projections having a width and an associated length into the piezoelectric polymer material; and (c) applying a metallic material to selected regions of at least one primary surface of the piezoelectric polymer material so as to cover at least a portion of each of the plurality of projections. For mass production applications, the forming step can be carried out by fabricating a shaping, forming, or molding tool that defines the channel geometry for each package. The tool can have raised projections and/or depressed formations. The forming step can be carried out by stamping the piezoelectric polymer material or the laminated material, which comprises the piezoelectric polymer material, onto the tool or the tool onto a layer or layers of piezoelectric polymer materials. Thus, in certain embodiments, the forming step is carried out by pressing the (which may be a laminated configuration) piezoelectric polymer material over a shaping tool having a plurality of raised projections thereon. The conductive material can be applied before or after the channel geometry forming step. The conductive material may be applied by applying a metallic coating onto a molding tool having a plurality of raised projections with a metallic coating and contacting the piezoelectric material with the molding/shaping tool to thereby transfer the metallic coating onto the desired surface (surfaces) of the elongated projections of the piezoelectric polymer material. Other methods of depositing the conductive pattern may be employed as described above.

In operation, generally described, the dry powder inhalers of the present invention have integrated, active energy piezoelectric polymer substrate multi-dose

drug packages that generate patient-assisted dispersal systems. The inhalers can be used for nasal and/or oral (mouth) respiratory delivery. The inhalable dry powder dose is packaged in a multi-dose dry powder drug package that includes a piezoelectric polymer substrate (such as PVDF) that flexes to deform rapidly and provide mechanical oscillation in an individually selectable signal path on the package. The signal path directs the signal to the region of the drug receptacle or well to cause the well to oscillate in cooperation with a user's inspiratory effort, and, thus, actively direct the dry powder out of the well and up into the exit flow path. The airflow rate and/or volume of a patient can be measured *in situ* dynamically during administration and the DPI can include a control system that provides adjustable energy output to the active piezoelectric polymer substrate dispersal element responsive to a user's inspiratory capabilities. In addition, the DPI control system may be a multi-purpose system that can administer a plurality of different types of dry powder substances, or formulations, such as different drugs. As such, the control system may be configured to adjust the energy delivered to the piezoelectric polymer substrate based on the type of substance and/or the flowability of the dry powder substance or drug being administered. The energy may be adjusted *in situ* based on considering both the user's inspiratory effort and the type of substance being administered. As a result, the powder can be actively dispersed into the exit flow path of the inhaler during the user's inspiratory activity without using pressurized propellants such as CFC's.

In addition, the piezoelectric polymer material may be configured as two piezoelectric polymer film layers separated by an intermediately positioned pliable core, all of which are concurrently deformable to flex by the application of voltage thereacross.

**Figure 22** is a block diagram of exemplary embodiments of data processing systems that illustrates systems, methods, and computer program products in accordance with embodiments of the present invention. The processor **410** communicates with the memory **414** via an address/data bus **448**. The processor **410** can be any commercially available or custom microprocessor. The memory **314** is representative of the overall hierarchy of memory devices containing the software and data used to implement the functionality of the data processing system **405**. The

memory **414** can include, but is not limited to, the following types of devices: cache, ROM, PROM, EPROM, EEPROM, flash memory, SRAM, and DRAM.

As shown in **Figure 22**, the memory **414** may include several categories of software and data used in the data processing system **405**: the operating system **452**; the application programs **454**; the input/output (I/O) device drivers **458**; the powder specific (vibratory) signal generator module **450**; and the data **456**. The data **456** may include a plurality of dry powder data **451** corresponding to particular or target signal parameters for each dry powder and/or patient inspiratory data, which may be obtained from an operator or stored by the inhaler and/or timing data that defines the meted dose amounts, flow rates, and open time for the dispensing port (allowing automatic control of the dispensing operation, dependent on the dry powder being dispensed). As will be appreciated by those of skill in the art, the operating system **452** of the inhaler and/or programmable inputs thereto may be any operating system suitable for use with a data processing system, such as OS/2, AIX, OS/390 or System390 from International Business Machines Corporation, Armonk, NY, Windows CE, Windows NT, Windows95, Windows98 or Windows2000 from Microsoft Corporation, Redmond, WA, Unix or Linux or FreeBSD, Palm OS from Palm, Inc., Mac OS from Apple Computer, LabView, or proprietary operating systems. The I/O device drivers **458** typically include software routines accessed through the operating system **452** by the application programs **454** to communicate with devices such as I/O data port(s), data storage **456** and certain memory **414** components and/or the dispensing system **420**. The application programs **454** are illustrative of the programs that implement the various features of the data processing system **405** and preferably include at least one application which supports operations according to embodiments of the present invention. Finally, the data **456** represents the static and dynamic data used by the application programs **454**, the operating system **452**, the I/O device drivers **458**, and other software programs that may reside in the memory **414.**

While the present invention is illustrated, for example, with reference to the powder-specific signal generator module **450** being an application program in **Figure 22**, as will be appreciated by those of skill in the art, other configurations may also be utilized while still benefiting from the teachings of the present invention. For example, the module **450** may also be incorporated into the operating system **452**, the

I/O device drivers **458** or other such logical division of the data processing system **405**. Thus, the present invention should not be construed as limited to the configuration of **Figure 22**, which is intended to encompass any configuration capable of carrying out the operations described herein.

The I/O data port can be used to transfer information between the data processing system **405** and the inhaler dispensing system **420** or another computer system or a network (*e.g.*, the Internet) or to other devices controlled by the processor. These components may be conventional components such as those used in many conventional data processing systems which may be configured in accordance with the present invention to operate as described herein.

While the present invention is illustrated, for example, with reference to particular divisions of programs, functions and memories, the present invention should not be construed as limited to such logical divisions. Thus, the present invention should not be construed as limited to the configuration of **Figure 22** but is intended to encompass any configuration capable of carrying out the operations described herein.

The flowcharts and block diagrams of certain of the figures herein illustrate the architecture, functionality, and operation of possible implementations of dry powder-specific dispensing and/or vibratory energy excitation means according to the present invention. In this regard, each block in the flow charts or block diagrams represents a module, segment, or portion of code, which comprises one or more executable instructions for implementing the specified logical function(s). It should also be noted that in some alternative implementations, the functions noted in the blocks may occur out of the order noted in the figures. For example, two blocks shown in succession may in fact be executed substantially concurrently or the blocks may sometimes be executed in the reverse order, depending upon the functionality involved.

In certain embodiments, the powder specific vibration energy signals are non-linear and the inhaler can include computer program code that automatically selectively adjusts the output of the vibration energy signal based on the identified dry powder being dispensed. The vibration energy output signals for the dry powders being dispensed can be based on data obtained from a fractal mass flow analysis or

other suitable analysis of the dry powder being administered to the user. The inhaler may be particularly suited to dispense low-density dry powder.

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. Although a few exemplary embodiments of this invention have been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. In the claims, means-plus-function clauses, where used, are intended to cover the structures described herein as performing the recited function and not only structural equivalents but also equivalent structures. Therefore, it is to be understood that the foregoing is illustrative of the present invention and is not to be construed as limited to the specific embodiments disclosed, and that modifications to the disclosed embodiments, as well as other embodiments, are intended to be included within the scope of the appended claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.

THAT WHICH IS CLAIMED IS:

1. A multi-dose dry powder package for holding pharmaceutical grade formulations of inhalable dry powder substances, comprising:

a platform body comprising a plurality of sealed blisters thereon and at least one thin piezoelectric polymer material layer forming at least a portion of each of the sealed blisters, wherein the sealed blisters comprise a respective at least one of a plurality of spatially separated discrete elongate dry powder channels having an associated length, width and height; and

a conductive material attached to selected portions of the piezoelectric polymer material including each of the regions corresponding to the blisters to define active energy releasing vibratory channels, and wherein, in operation, the blisters are adapted to be selectively activated to vibrate upon receipt of an electrical input.

2. A package according to Claim 1, in combination with an input signal generating circuit that is adapted to operatively engage each of the blisters, the input signal generating circuit configured to selectively provide the electrical input to selectively flex a portion of the blisters responsive to the electrical input.

3. A package according to Claim 2, wherein, in operation, the electrical input is configured to flex at least one of the blisters by applying a non-linear vibration input signal thereto, and wherein the non-linear input signal selected to represent *a priori* flow characteristic frequencies of the dry powder formulation held in the package.

4. A package according to Claim 3, wherein the non-linear vibration input signal comprises a plurality of different selected frequencies that correspond to the flow characteristic frequencies of the dry powder formulation held in the package.

5. A package according to Claim 4, wherein the non-linear vibration input signal is formed by the superimposition of the plurality of different selected frequencies.

6. A package according to Claim 2, wherein the input generating circuit electrical input is configured to flex the channels by applying an amplitude modulated frequency selected to represent *a priori* flow characteristic frequencies of the dry powder formulation held in the package

7. A package according to Claim 1, further comprising a quantity of dry powder substance disposed in the elongate channels, and wherein the length of the elongate channels is selected to correspond to predetermined flow characteristics of the dry powder substance so as to promote the energy exchange between the elongate channel and the dry powder during active inhalation delivery.

8. A package according to Claim 1, wherein the platform body is configured as a substantially flat disk, with the elongate channels circumferentially spaced apart about a selected primary surface of the disk.

9. A package according to Claim 8, wherein the elongate channels have a curvilinear profile when viewed from the top.

10. A package according to Claim 9, wherein the elongate channels are substantially pear-shaped.

11. A package according to Claim 8, wherein the elongate channels comprise a floor that comprises the piezoelectric polymer material, and wherein, in operation, the floor flexes in response to the electrical input.

12. A package according to Claim 1, wherein each blister has a quantity of inhalable dry powder therein, wherein each sealed blister comprises a floor defined by a respective one of the elongate channels and a ceiling overlying the elongate channel, the ceiling and floor configured to encase the dry powder in the elongate channel, and wherein the ceiling has an outwardly extending protrusion positioned on a forward portion of the elongate channel that terminates into a substantially planar portion over the rearward portion of the elongate channel.

13. A package according to Claim 1, wherein the platform body is configured as a thin sheet of scrolled flexible material rolled about two spaced-apart tension rods.

14. A package according to Claim 1, in combination with a second multi-dose dry powder package comprising:

a platform body comprising a thin piezoelectric polymer material layer forming at least a portion of a plurality of spatially separated blisters formed by discrete elongate dry powder channels having an associated length, width and height; and

a conductive material attached to selected portions of the piezoelectric polymer material including each of the regions corresponding to the elongate dry powder channels to define active energy releasing vibratory channels, and wherein, in operation, the elongate channels are adapted to selectively individually activated to vibrate upon receipt of an electrical input,

wherein the first and second dry powder packages are held in proximately-spaced stacked relationship during use.

15. A stacked package according to Claim 14, further comprising a first dry powder substance disposed in the elongate channels of the first package and a second different dry powder substance disposed in the elongate channels of the second package, and wherein, during use, both of the first and second substances are substantially concurrently dispensed to the patient.

16. A stacked package according to Claim 14, wherein the first and second packages are held so that centers thereof are aligned.

17. A stacked package according to Claim 14, wherein the first and second packages are held so that centers are offset.

18. A stacked package according to Claim 14, further comprising a third package, the third package comprising:

a platform body comprising a thin piezoelectric polymer material layer forming at least a portion of a plurality of blisters, each blister comprising a respective one of spatially separated discrete elongate dry powder channels having an associated length, width and height; and

a conductive material attached to selected portions of the piezoelectric polymer material including each of the regions corresponding to the elongate dry powder channels to define active energy releasing vibratory channels, and wherein, in operation, the elongate channels can be selectively individually activated to vibrate upon receipt of an electrical input,

wherein the first, second, and third dry powder packages each have centers, and wherein the first, second, and third packages are held in closely adjacent stacked relationship and with each center offset from the others.

19. A package according to Claim 1, wherein the package platform further comprises a plurality of airflow and/or differential pressure sensors, a respective one located proximate each elongate channel, wherein the sensors are selectably activatable and configured such that, during use, the sensors provide data used to determine user airflow rate *in situ* during the activation of a respective channel.

20. A package according to Claim 1, wherein the elongate channels have an associated floor and opposing sidewalls, and wherein the sidewalls and floor of the elongate channels comprise the piezoelectric polymer.

21. A package according to Claim 1, wherein the blister elongate channels have an associated ceiling comprising the piezoelectric polymer.

22. A package according to Claim 1, wherein the elongate channels have an associated floor, ceiling, and opposing sidewalls, and wherein the sidewalls, floor, and ceiling of the elongate channels comprise the piezoelectric polymer.

23. A package according to Claim 1, wherein the elongate channels have a floor that slopes downwardly in the direction of outward flow.

24. A package according to Claim 23, wherein the elongate channels have a depth that increases in the forward flow direction.

25. A package according to Claim 1, wherein the elongate channels have a depth that decreases in the forward flow direction.

26. A package according to Claim 1, wherein the elongate channels comprise a powder basin with a depth that is greater than rearward and forward portions of the channel.

27. A package according to Claim 1, wherein the blisters comprise a cover portion that overlies and seals each elongate channel with a quantity of dry powder held therein, wherein the cover includes a plurality of arch portions that extend outwardly away from the elongate channels, a respective one of the arch portions being positioned over a forward portion of a corresponding one of the elongate channels.

28. A package according to Claim 1, wherein the elongate channels have a first rearward curvilinear portion that terminates into a second forward curvilinear portion, and wherein the second curvilinear portion has a smaller perimeter and is disposed downstream of the first curvilinear portion in the direction of flow.

29. A package according to Claim 3, wherein the non-linear input signal is a low energy input signal having a plurality of superpositioned modulating frequencies, and wherein the non-linear input signal comprises frequencies in the range of between about 10Hz to 1000kHz.

30. A package according to Claim 3, wherein the non-linear input signal comprises carrier frequencies in the range of between about 15kHz to 50kHz.

31. A package according to Claim 1, wherein the elongate channels have an associated ceiling that is scored at an end portion thereof to preferentially predispose the end portion to split upon exposure to a blunt pressure or force.

32. A dry powder inhaler, comprising:

an elongate body having opposing first and second outer primary surfaces with a cavity therebetween and having opposing top and bottom end portions;

a multi-dose sealed blister package holding a plurality of discrete meted doses of a dry powder inhalable product located in the cavity of the elongate body;

an inhalation port formed in the bottom end portion of the elongate body, the inhalation port configured to be in fluid communication with at least one of the discrete meted doses during use; and

a cover member that is pivotally attached to the elongate body and moves between a first closed position to overlie the inhalation port at the bottom end portion of the body during periods of non-use and a second open position away from the inhalation port during periods of use to allow a user to access the inhalation port.

33. A dry powder inhaler according to Claim 32, wherein the cover member has a length and a width and the elongated body has a length and a width, and wherein the cover member length is greater than a major portion of the length of the elongated body and the cover member width is less than the width of the elongate body.

34. A dry powder inhaler according to Claim 32, wherein the cover member has two opposing first and second end portions, the first end portion being pivotally attached to an upper portion of the elongated body, the cover having a major portion with a substantially planar profile and a downwardly extending arcuately shaped second end portion.

35. A dry powder inhaler according to Claim 34, wherein the arcuately shaped end portion extends a distance to snugly abut and wrap around and conform to the bottom portion of the elongate body.

36. A dry powder inhaler according to Claim 34, wherein the cover member is an elastomeric flexible cover.

37. A dry powder inhaler according to Claim 32, wherein the first primary surface of the elongate body comprises a window that overlies a portion of the multidose package.

38. A dry powder inhaler according to Claim 37, wherein the multidose package comprises externally visible indices of the dose number that are visible through the window during use.

39. A dry powder inhaler according to Claim 37, wherein the multidose package includes at least one of a visible or audible alert warning that alerts the user when the multi-dose package approaches the last few remaining doses.

40. A dry powder inhaler according to Claim 37, wherein the cover member is pivotally attached to pivot about an axis that extends through and normal to the window.

41. A dry powder inhaler according to Claim 40, wherein said elongate body is formed from two matably detachable first and second shells, the first shell defining the first primary surface and the second shell defining the second primary surface.

42. A dry powder inhaler according to Claim 32, wherein the elongate body further comprises a depressible user activation button accessible via the first surface and a dose advancing knob on the opposing side of the elongate body in communication with the multi-dose package.

43. A dry powder inhaler according to Claim 42, wherein the cover member has a major portion that is substantially planar with an outwardly projecting portion formed therein, the outwardly projecting portion configured to overlie the activation button on the first surface of the elongate body when the cover member is closed over the inhalation port to inhibit inadvertent activation.

44. A dry powder inhaler according to Claim 32, wherein with the cover member in the closed position, the elongate body has a thin profile with substantially flat first and second primary surfaces defining a pocket-sized inhaler that fits into the pocket of a garment worn by a user.

45. A dry powder inhaler according to Claim 32, wherein the inhalation port is formed in a mouthpiece that is releaseably attached to the elongate body bottom portion thereby allowing periodic cleaning or replacement.

46. A dry powder inhaler according to Claim 32, further comprising:

control circuitry held in the elongated body; and

a battery operatively associated with the control circuitry,

wherein the multi-dose blister package comprises:

a platform body comprising at least one piezoelectric polymer material layer forming at least a portion of each of a plurality of spatially separated discrete blisters having elongate dry powder channels having an associated length, width and height; and

a conductive pattern configured on the platform body so as to be in communication with the control circuitry, the conductive pattern being attached to selected portions of the piezoelectric polymer material including each of the regions corresponding to the blisters to define active energy releasing vibratory channels, wherein, in operation, the control circuitry generates an electrical input that is transmitted via the conductive pattern to flex the piezoelectric polymer material associated with at least one selected blister and vibrate the dry powder in the associated at least one elongate channel.

47. A dry powder inhaler according to Claim 46, further comprising a quantity of dry powder substance disposed in the elongate channels, and wherein the length of the elongate channels is selected to correspond to predetermined flow characteristics of the dry powder substance so as to promote the energy exchange between the elongate channel and the dry powder during active inhalation delivery.

48. A dry powder inhaler according to Claim 46, wherein the control circuitry is configured to generate an amplitude-modified frequency signal corresponding to *a priori* flow characteristics of the dry powder being dispensed to selectively vibrate powder in the selected blister elongate flow channel.

49. A dry powder inhaler according to Claim 46, wherein the control circuitry is configured to generate a non-linear signal to selectively vibrate the powder in a selected blister elongate flow channel.

50. A dry powder inhaler according to Claim 49, wherein the non-linear signal comprises a plurality of predetermined superimposed frequencies selected according to *a priori* flow characteristics of the dry powder being dispensed.

51. A dry powder inhaler according to Claim 46, wherein the dry powder inhaler is configured to serially accept and dispense inhalable dry powder from a plurality of different blister packages, each blister package having elongated channels of different lengths.

52. A dry powder inhaler according to Claim 46, wherein the control circuitry is configured to detect a predetermined electrical parameter associated with the position of one of the elongate channels with respect to the inhalation port to affirm proper alignment before allowing active dispersement of the dry powder dose.

53. A dry powder inhaler according to Claim 52, wherein the electric parameter is the capacitance of the piezoelectric polymer material.

54. A dry powder inhaler according to Claim 46, wherein, in operation, the control circuitry is configured to apply the electrical input so that an excitation voltage differential is transmitted to a selected one of the elongated channels to cause said piezoelectric material layer to flex thereat to promote resonance of the dry powder and actively disperse a dry powder pharmaceutical drug from the elongated channel through the inhalation port.

55. A dry powder inhaler according to Claim 46, wherein said piezoelectric material is a thin film PVDF laminated to at least one different material layer, the different material layer configured to allow the blisters to be formed into and substantially retain a desired shape.

5

56. A dry powder inhaler according to Claim 32, wherein the dry powder is a low density dry powder, and wherein the inhalable dry powder held in the multi-dose blister package comprises active ingredient particulate sizes of between about 0.5-8.0 μm.

10

57. A dry powder inhaler according to Claim 32, wherein the dry powder is formulated in an amount of between about 5-15 mg with an active ingredient concentration of at least between about 5-10%.

15 58. A dry powder inhaler according to Claim 46, wherein a respective one of the elongate channels forms a floor for a corresponding one of the blisters, wherein the blisters each including a ceiling overlying the respective elongate channel, wherein the ceiling includes a semi-spherical portion that extends away from the elongate channel and is disposed on a forward portion of the elongate channel.

20

59. A dry powder inhaler according to Claim 46, wherein a respective one of the elongate channels forms a ceiling or floor for one of the blisters, the inhaler further comprising a dose releasing member disposed in the inhaler and configured to advance toward, contact, and retract away from one of the floor or ceiling of the

25 multi-dose package to thereby form an opening in the blister.

60. A dry powder inhaler according to Claim 58, wherein the dose releasing member has a forward edge portion that has a shape that corresponds to the shape of the semi-spherical portion of the ceiling.

30

61. A dry powder inhaler according to Claim 46, wherein a respective one of the elongate channels forms a floor for one of the blisters, wherein the elongate channels have an internal cavity profile, the inhaler further comprising a dose

releasing member disposed in the inhaler to advance toward and retract away from the ceiling side of the multi-dose package, and wherein the dose releasing member has a forward edge portion that has a shape that corresponds to the shape of the cavity profile.

62. A method for fabricating a multi-dose disposable dry powder blister package, comprising:

providing a piezoelectric polymer material;

concurrently forming a plurality of elongated projections or depressions having a width and an associated length into the piezoelectric polymer material; and

applying a metallic material pattern to selected regions of at least one primary surface of the piezoelectric polymer material so as to extend over at least a portion of each of the plurality of projections or depressions.

63. A method according to Claim 62, wherein said forming step is carried out by stamping.

64. A method according to Claim 62, wherein said forming step is carried out by pressing the piezoelectric polymer material over a shaping tool having a plurality of raised projections thereon.

65. A method according to Claim 62, wherein said applying step is carried out before the forming step.

66. A method according to Claim 62, wherein said applying step is carried out after the forming step.

67. A method according to Claim 63, wherein said forming step forms projections, and wherein said applying step comprises:

applying a metallic coating onto a molding tool having a plurality of raised projections; and

contacting the piezoelectric material with the molding tool to thereby transfer the metallic coating onto the elongated projections of the piezoelectric polymer material.

68. A method of administering an inhalable dry powder product to a subject, comprising:

oscillating piezoelectric polymer material associated with at least a portion of at least one sealed encased elongated channel having opposing first and second end portions and a quantity of dry powder product therein with a predetermined electrical signal;

disrupting the seal associated with the elongated channel at the second end portion;

directing the dry powder product to flow through the elongated channel to exit at the second end portion so that a major portion of the dry powder substance repeatedly contacts the oscillating piezoelectric material at a plurality of locations along the elongated channel, wherein, the oscillating and directing steps impart energy to the dry powder product to cause the dry powder product to vibrate; and

releasing the inhalable dry powder to a subject upon inhalation.

69. A method according to Claim 68, wherein the oscillating step is carried out by applying an amplitude-modified frequency voltage signal to the piezoelectric polymer material.

70. A method according to Claim 69, wherein the amplitude-modified input signal is selected based on an *a priori* flow evaluation of the dry powder formulation held in the package.

71. A method according to Claim 68, wherein the oscillating step is carried out by applying a non-linear voltage signal to the piezoelectric polymer material.

72. A method according to Claim 71, wherein the non-linear vibration input signal comprises a plurality of different superimposed frequencies that

correspond to *a priori* flow characteristic frequencies of the dry powder formulation held in the package.

73. A method according to Claim 68, further comprising automatically vibrating the elongated channel prior to said disrupting step to thereby prime the channel for active dispersal.

74. A method according to Claim 68, wherein the sealed elongated channel comprises a cavity with a floor and an overlying covering, wherein said disrupting step comprises releasing a forward edge portion of the floor and forcing the released edge portion to reside above the cavity proximate the ceiling and to substantially take on the shape of the ceiling.

75. A method according to Claim 68, wherein the sealed elongated channel comprises a cavity with a floor and an overlying covering, wherein said disrupting step comprises releasing a forward edge portion of the ceiling and forcing the released edge portion to reside in the cavity proximate the floor and to substantially take on the shape of the cavity floor.

76. A method according to Claim 68, wherein said elongate channel comprises a floor and ceiling covering, and wherein said disrupting step comprises advancing a dose release member substantially perpendicular to the direction of inhalation flow and introducing an aperture into the floor.

77. A method according to Claim 74, wherein said releasing and forcing steps are carried out by advancing a dose release member with an arched upper edge portion substantially perpendicular to the direction of inhalation flow and introducing an aperture into the ceiling.

78. A method according to Claim 74, wherein said releasing and forcing steps are carried out by advancing a dose release member with an arched upper edge portion substantially perpendicular to the direction of inhalation flow and introducing an aperture into the floor.

79. A method according to Claim 68, wherein the sealed encased elongated channel is disposed on a thin strip of scrolled material that holds a plurality of sealed elongated dry powder containing channels, and said method further comprises rolling the scrolled material to position a selected sealed encased elongated channel in a dispensing orientation.

80. A method according to Claim 68, wherein the sealed encased elongated channel is disposed on a thin disk that includes a plurality of sealed elongated dry powder containing channels.

81. A method according to Claim 68, further comprising concurrently oscillating a second piezoelectric polymer material forming at least a portion of a second sealed encased elongated channel, the second elongated channel having opposing first and second end portions and a quantity of dry powder product therein;

disrupting the seal associated with the second elongated channel at the second end portion;

directing the dry powder product to flow through the second elongated channel to exit at the second end portion so that a major portion of the dry powder substance repeatedly contacts the oscillating piezoelectric material at a plurality of locations along the elongated channel; and

releasing the second inhalable dry powder aerosol to a subject upon inhalation concurrently with the first inhalable dry powder aerosol.

82. A method according to Claim 81, wherein the second oscillating and directing steps impart energy to the dry powder in the second elongated channel to cause the dry powder to vibrate at a desired amplitude modified frequency to generate a second inhalable dry powder aerosol.

83. A method according to Claim 81, wherein the second oscillating and directing steps impart energy to the dry powder in the second elongated channel to cause the dry powder to vibrate with a non-linear motion to generate a second inhalable dry powder aerosol.

84. A method according to Claim 68, wherein the at least one sealed encased elongated channel is two, each disposed on a blister package that is stacked in spaced apart alignment and includes plurality of sealed elongated dry powder containing channels.

85. A method according to Claim 84, further comprising compressing the two blister packages toward each other and substantially concurrently releasing the contents of two different elongated channels holding two meted different dry powder products to thereby combine two meted amounts of dry powder into a single combined inhalable aerosol.

86. A method according to Claim 69, wherein the oscillating step electrical signal comprises a frequency that is between about 10-200Hz.

87. A method according to Claim 71, wherein the non-linear input signal is a low energy input signal having a plurality of superpositioned modulating frequencies.

88. A method according to Claim 87, wherein the non-linear input signal comprises frequencies in the range of between about 10Hz to 1000kHz.

89. A method of administering an inhalable dry powder product to a subject, comprising:

providing an inhaler with a multiple dose blister package comprising piezoelectric polymer material that is associated with a plurality of discrete sealed blisters holding respective dry powder doses;

priming a selected portion of the package to vibrate the dry powder in at least one selected sealed blister proximate in time to an intended inhalation delivery thereof; then

introducing an opening in the at least one selected blister;

vibrating the at least one selected blister by a applying an input signal to the piezoelectric polymer material proximate the selected blister; and

releasing the inhalable dry powder to a subject upon inhalation.

90. A method according to Claim 89, wherein the introducing and vibrating steps are carried out within about 50 ms of each other.

91. A method according to Claim 90, wherein the introducing step is carried out before the vibrating step.

92. A method according to Claim 90, wherein the introducing step is carried out after the vibrating step is initiated.

93. A method according to Claim 89, wherein the introducing step is carried out during the vibrating step.

94. A method according to Claim 89, further comprising:

aligning a selected blister with an inhalation port in the inhaler; and

monitoring an alignment parameter associated with the position of the blister to confirm proper positional alignment of the blister prior to initiating the opening step.

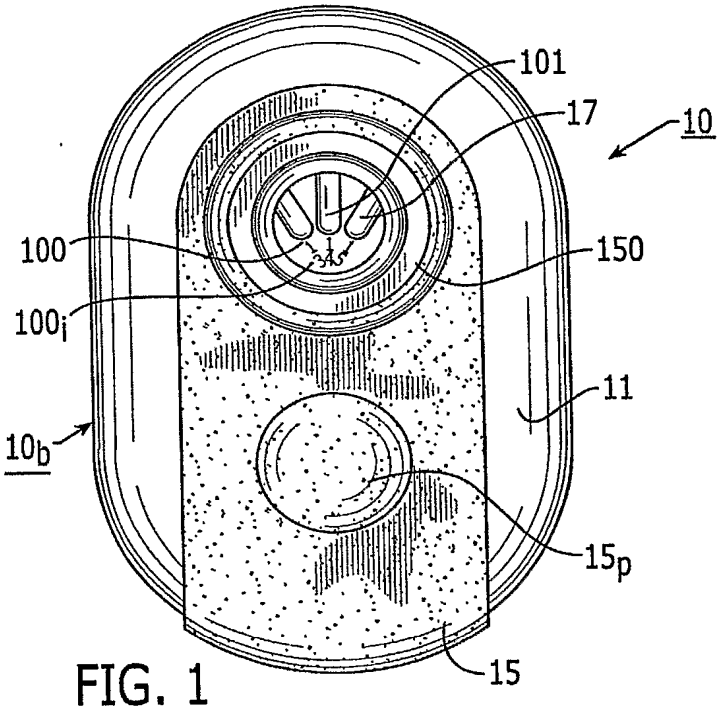



FIG. 1

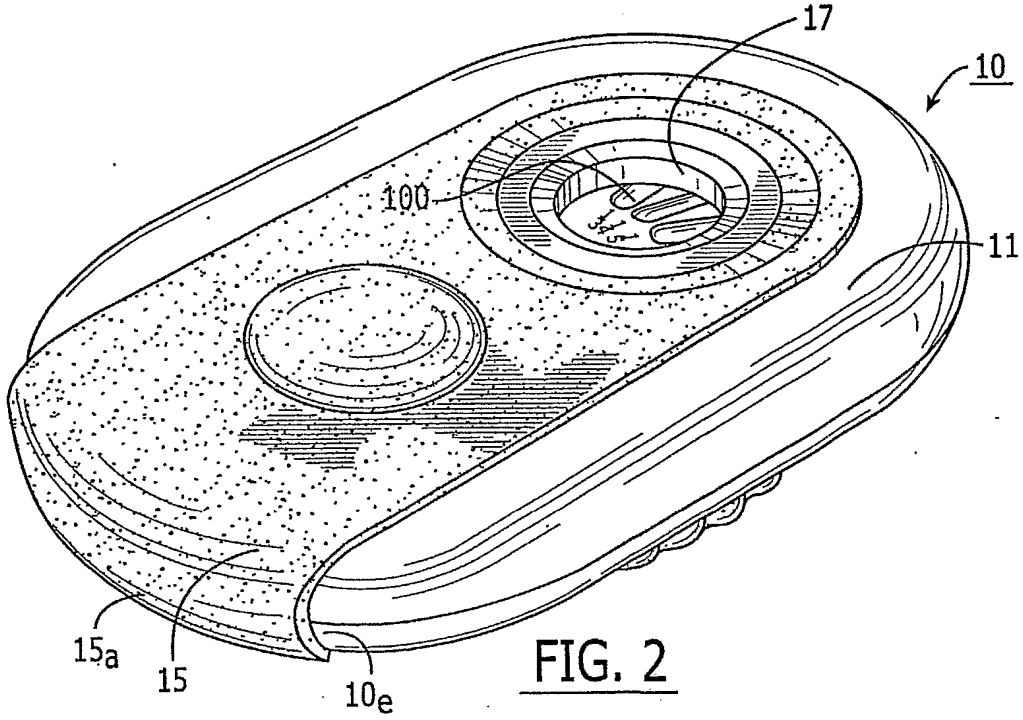



FIG. 2

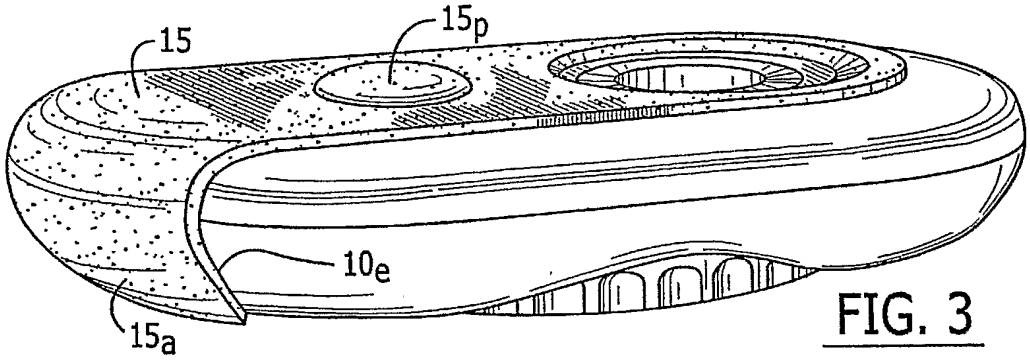



FIG. 3

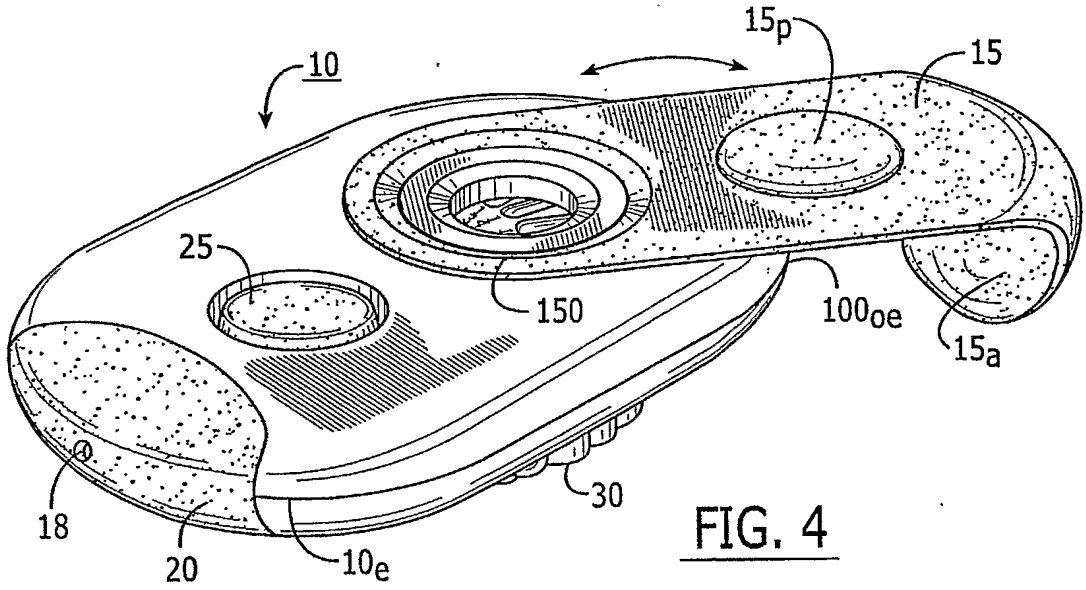



FIG. 4

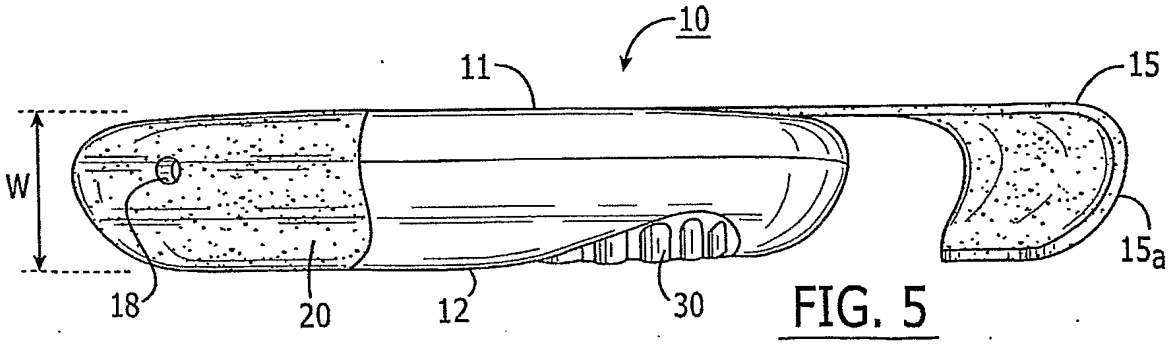



FIG. 5

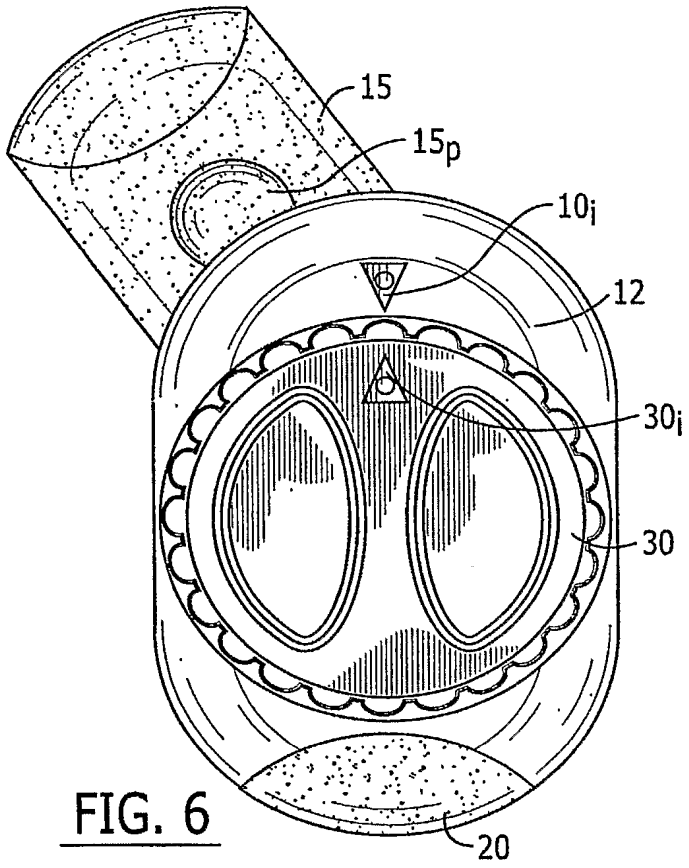



FIG. 6

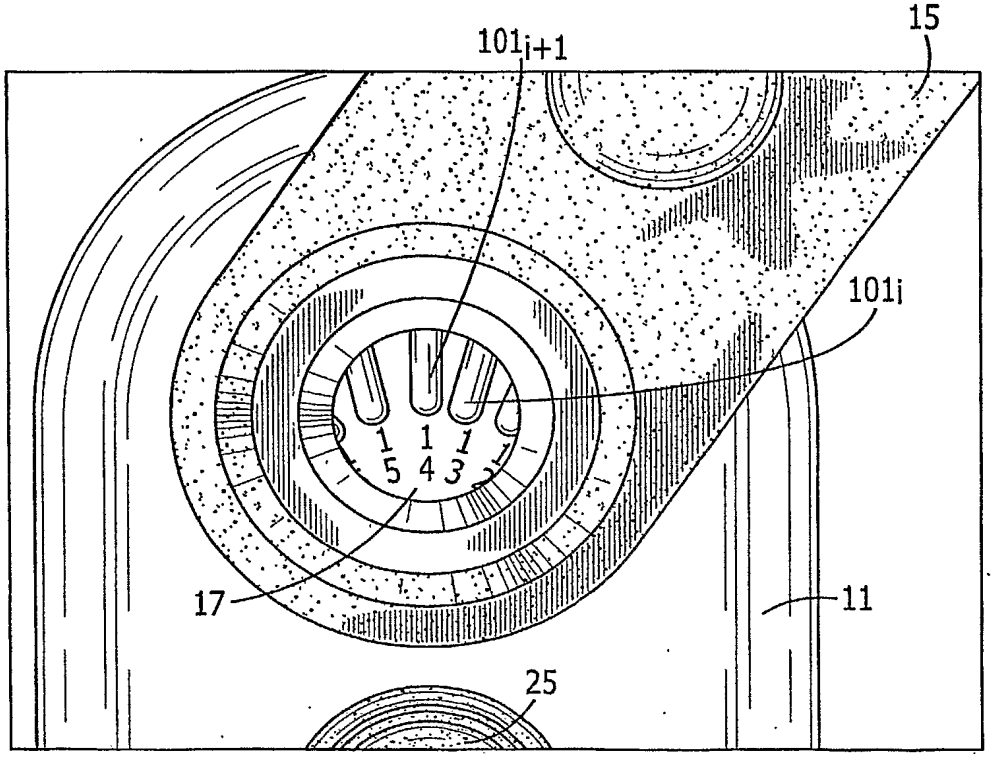



FIG. 7

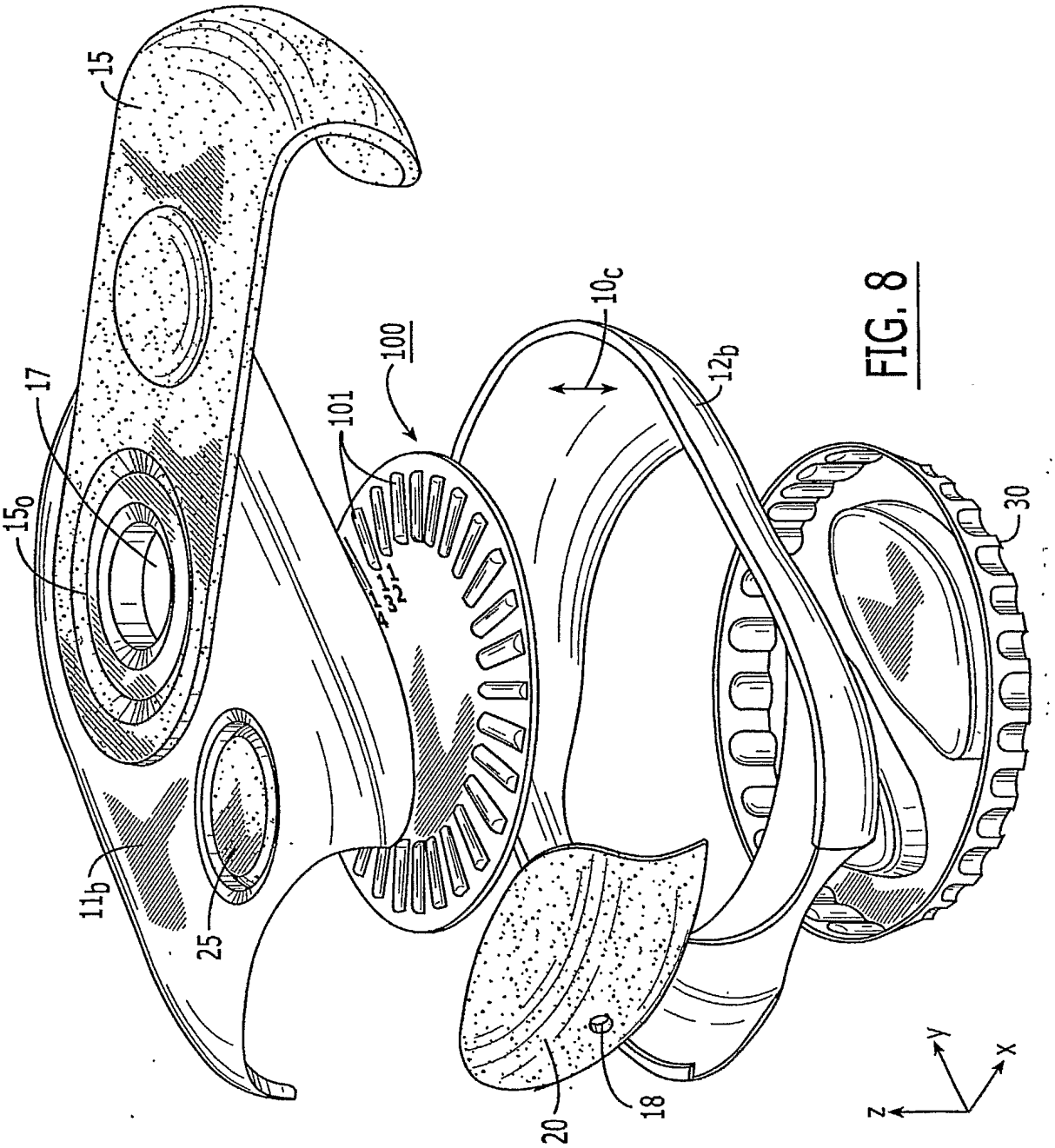



FIG. 8

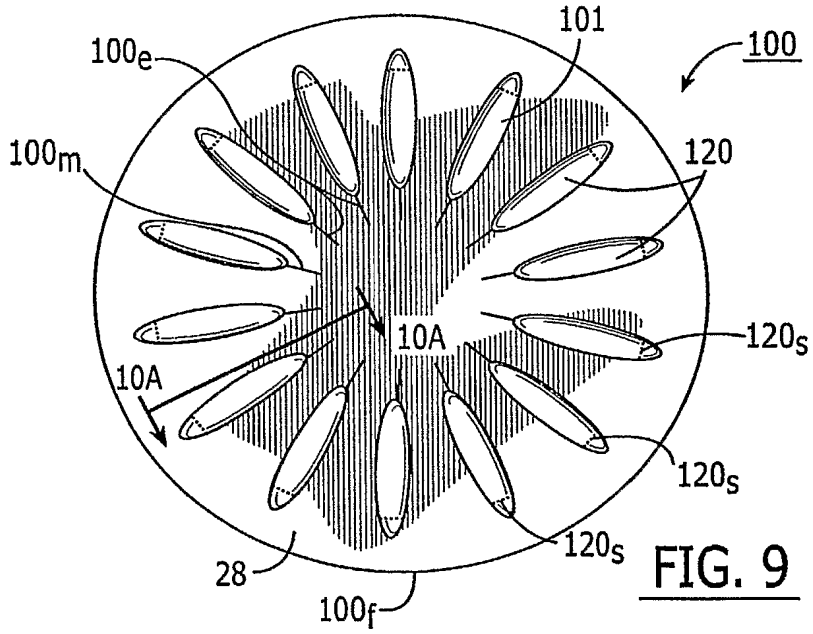



FIG. 9

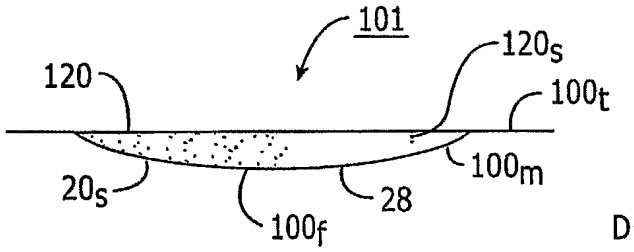



FIG. 10A

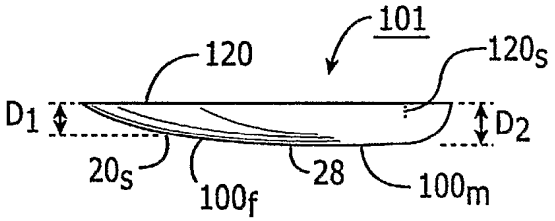



FIG. 10B

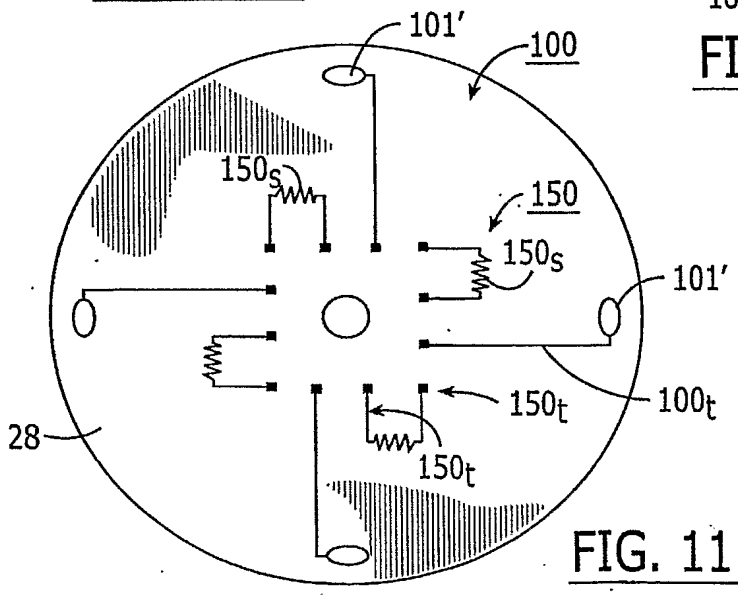



FIG. 11

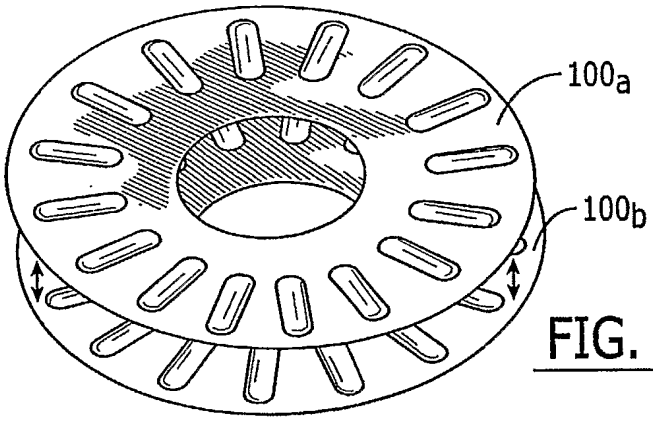



FIG. 12A

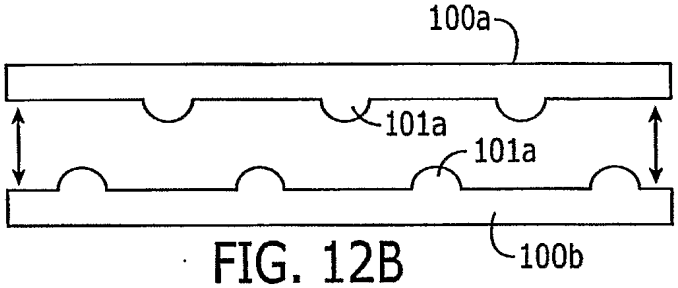



FIG. 12B

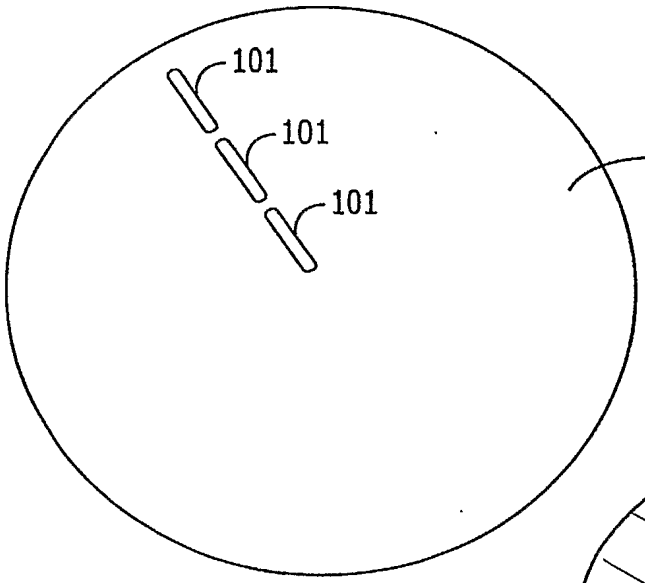



FIG. 12C

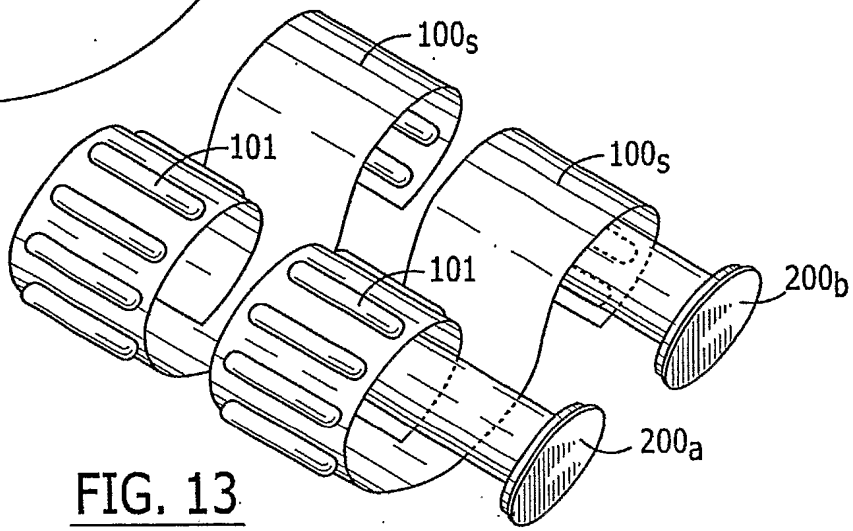



FIG. 13

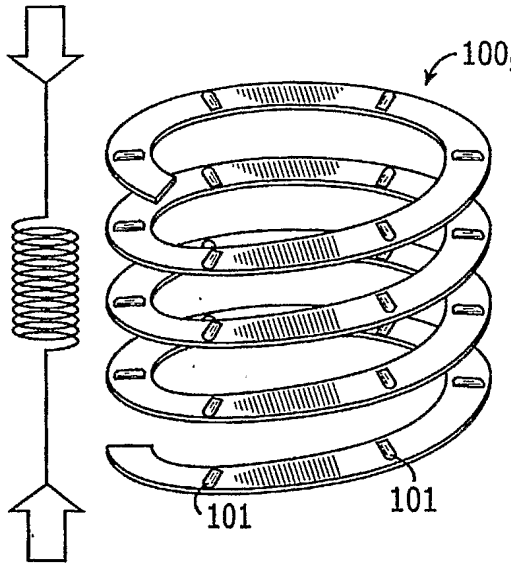



FIG. 14A

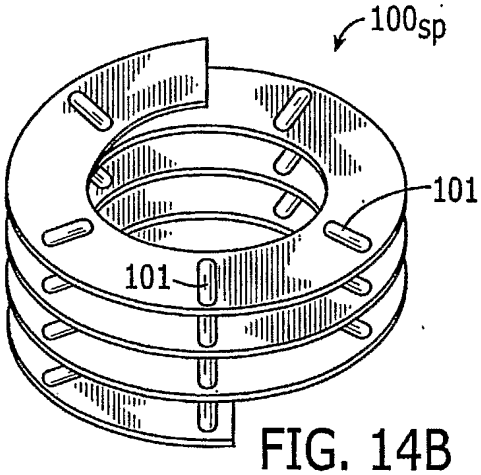



FIG. 14B

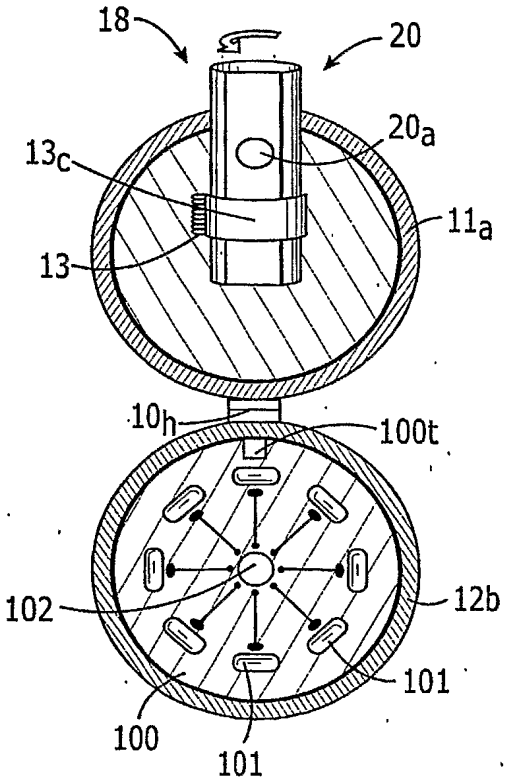



FIG. 15A

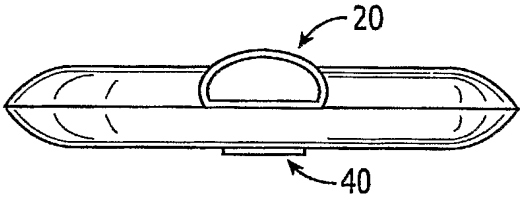



FIG. 15B

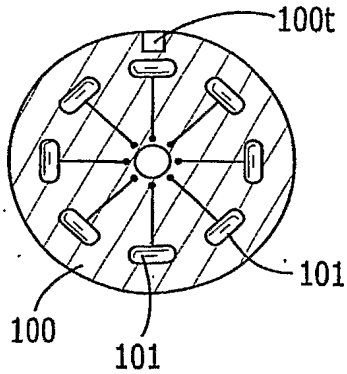



FIG. 15C

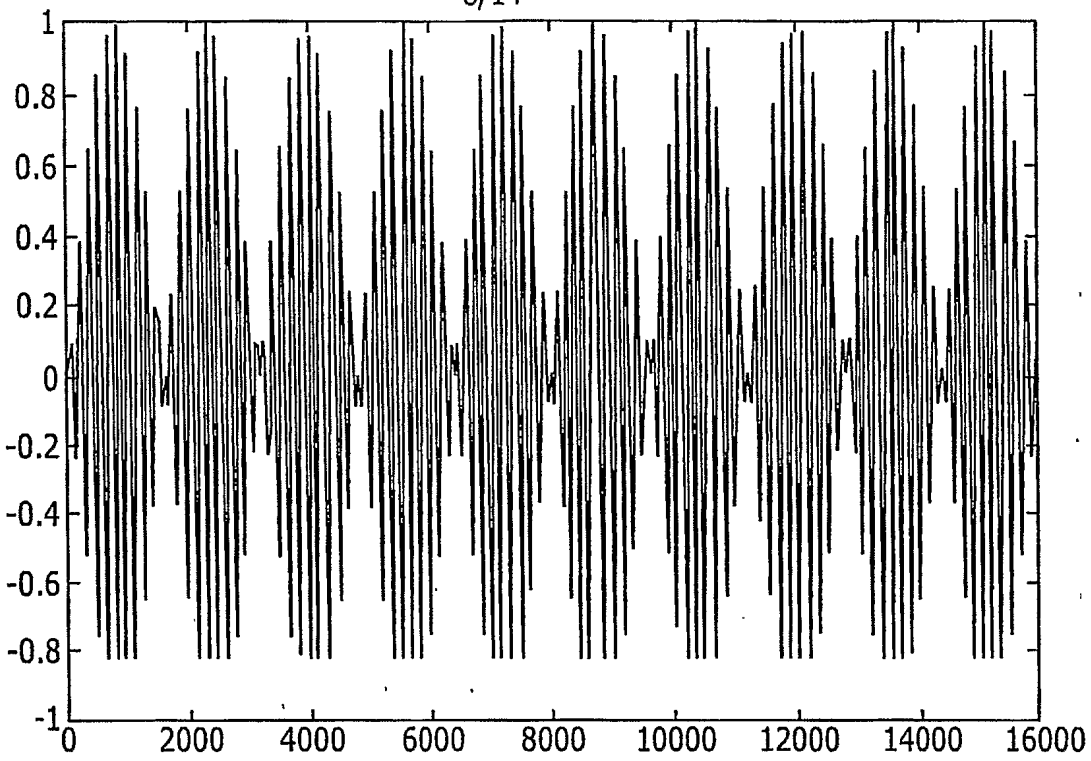



FIG. 16A

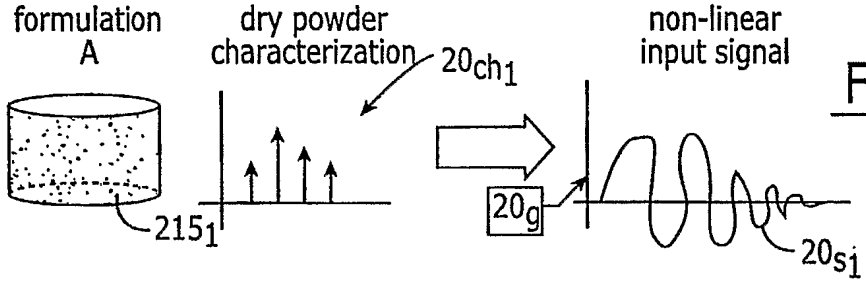



FIG. 16B

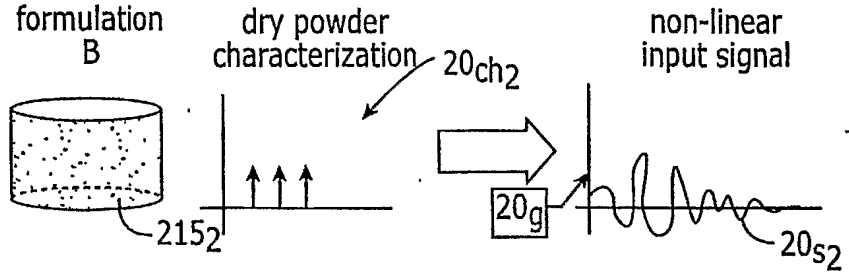



FIG. 16C

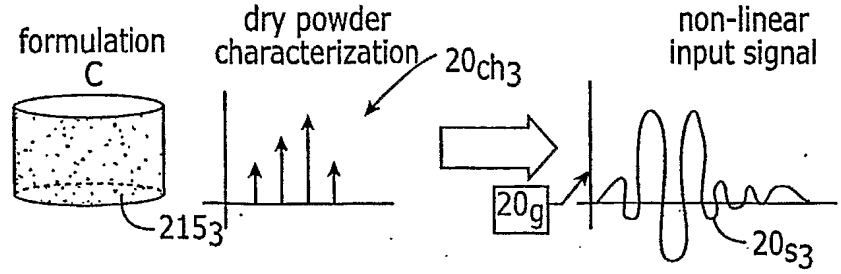



FIG. 16D

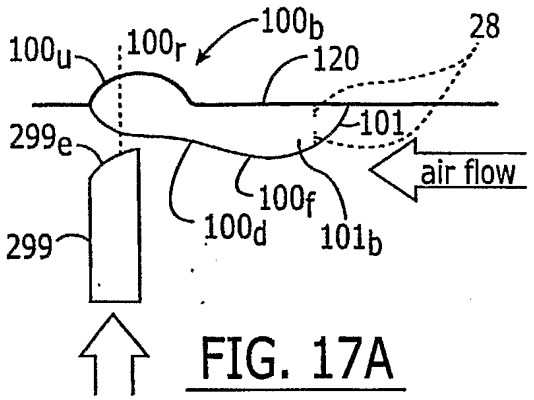



FIG. 17A

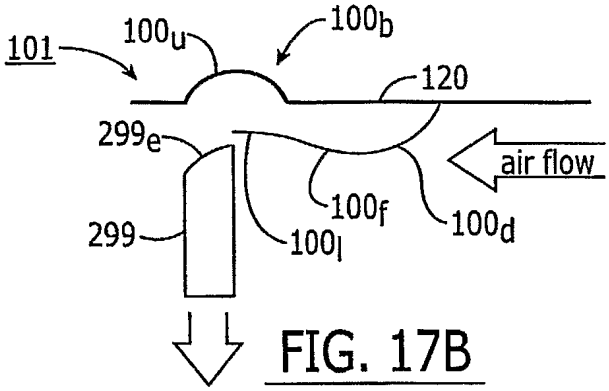



FIG. 17B

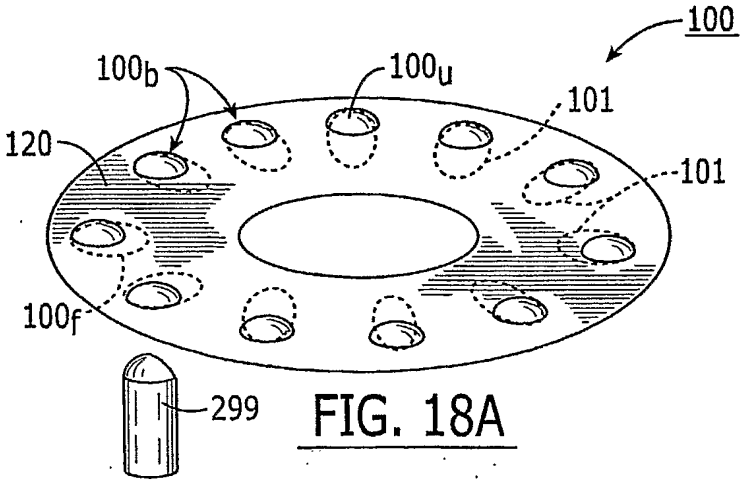



FIG. 18A

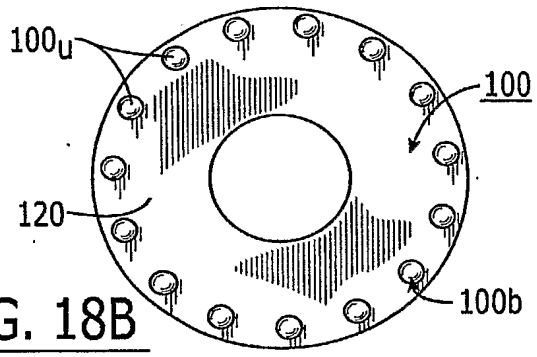



FIG. 18B

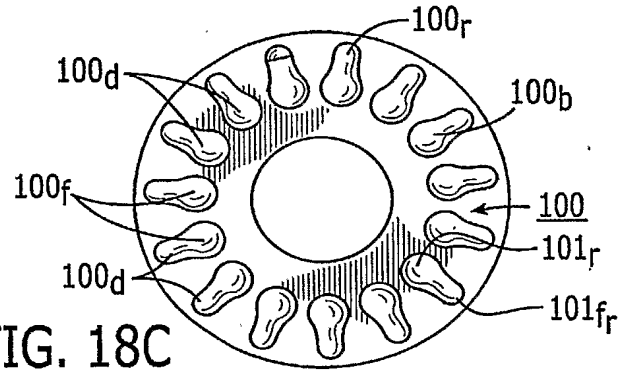



FIG. 18C

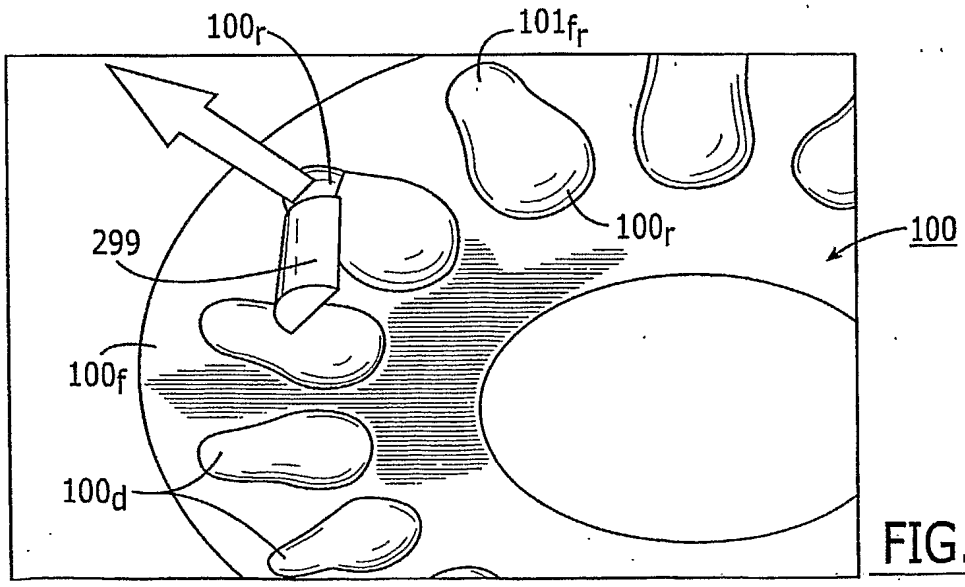



FIG. 18D

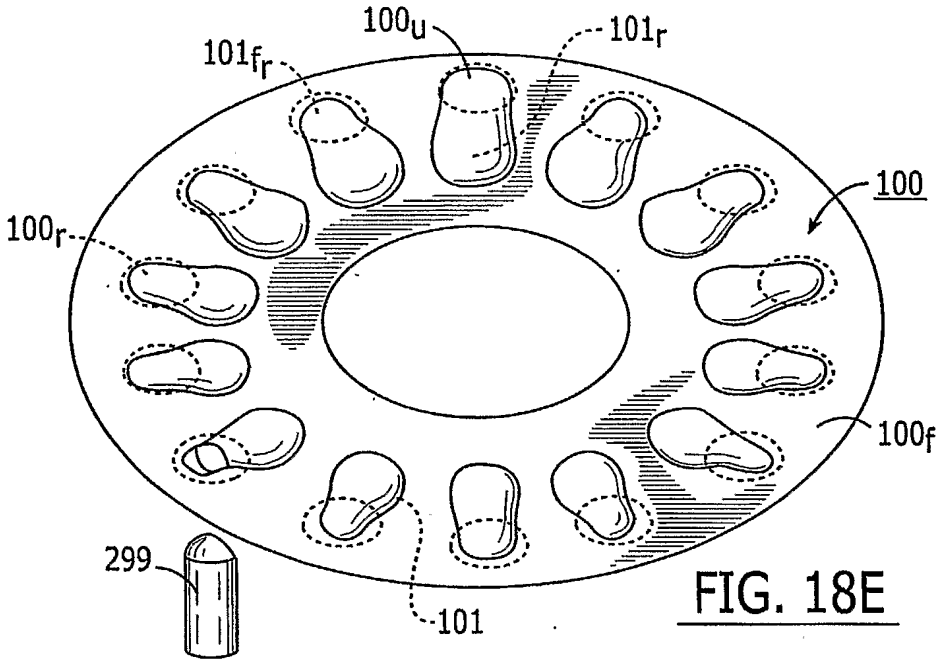



FIG. 18E

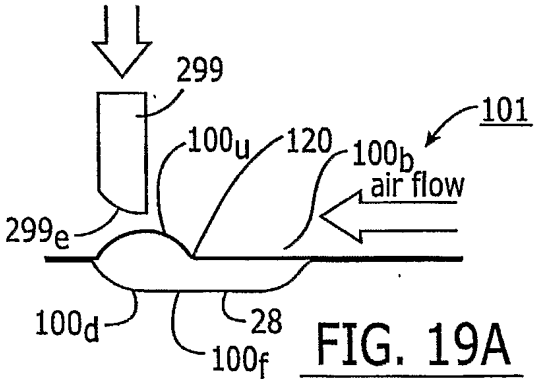



FIG. 19A

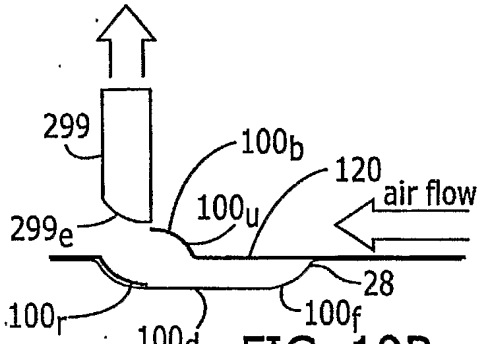



FIG. 19B

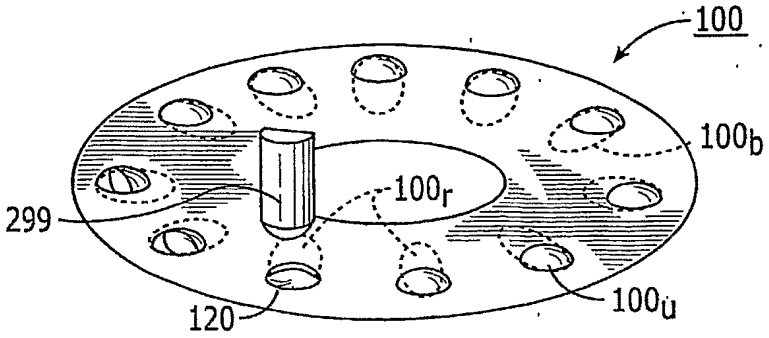



FIG. 20A

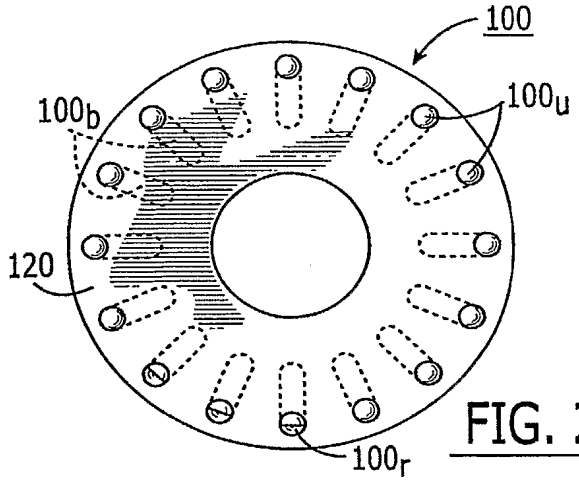



FIG. 20B

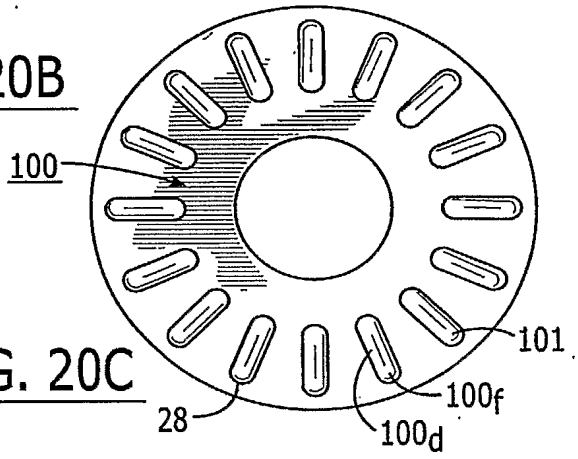



FIG. 20C

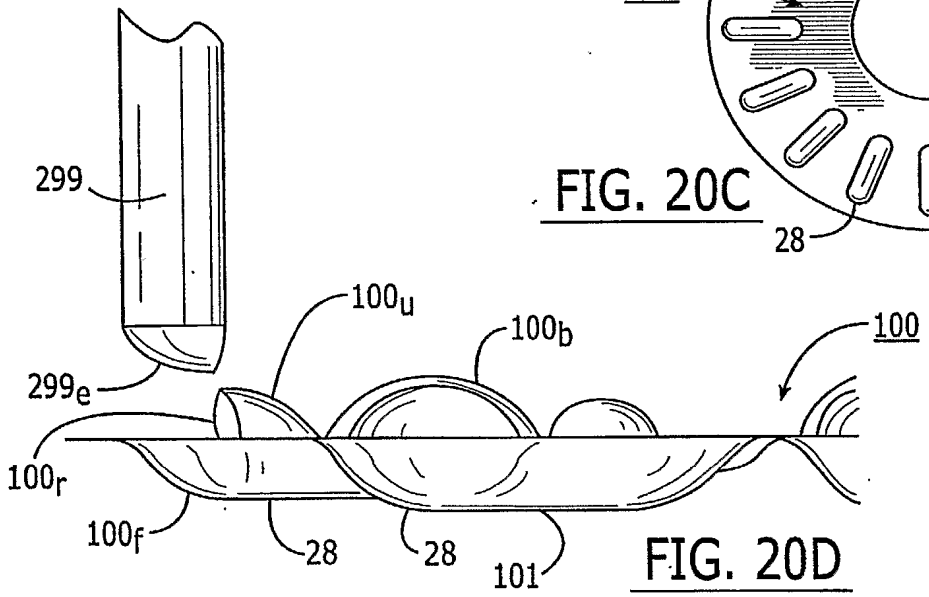



FIG. 20D

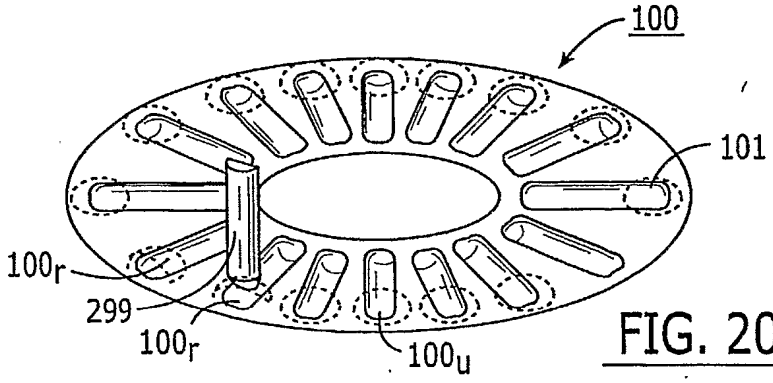
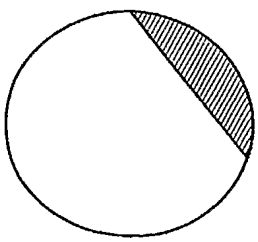



FIG. 20E

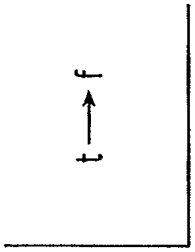
SIGNAL GENERATION

FIG. 21A



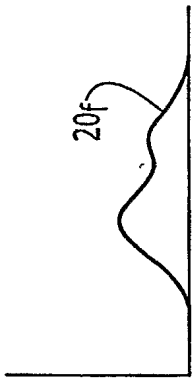
Measure time between avalanches for powders in rotating drum

FIG. 21B




Convert time to frequency space

FIG. 21C




Plot distribution of frequencies

FIG. 21D


Record top six most observed frequencies, typically representing 75% of distribution

FIG. 21E


Superimpose these six frequencies to construct a single superposition signal (can include step of adjusting relative amplitudes)

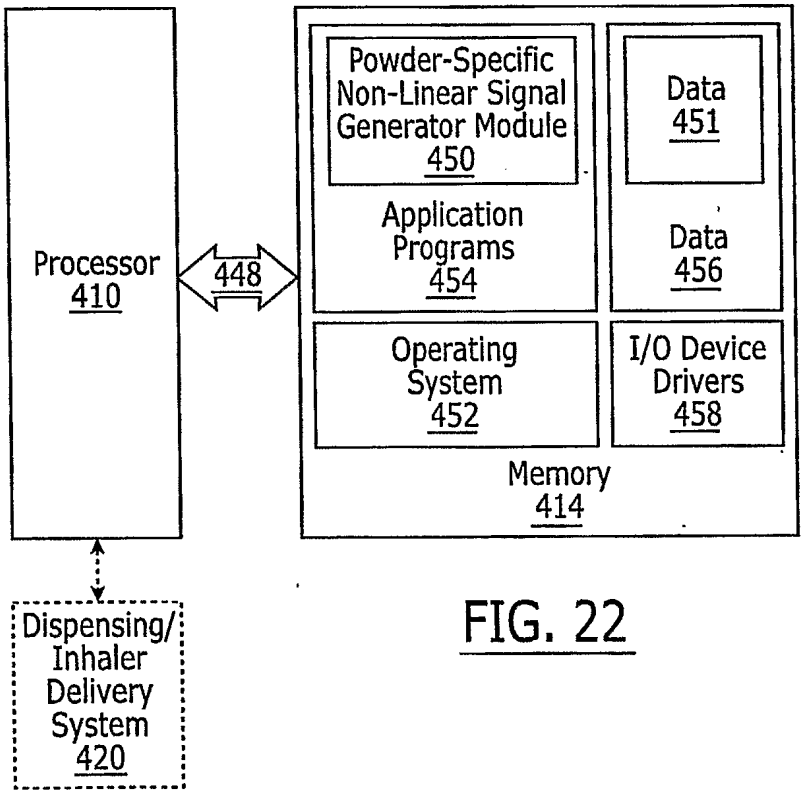

Processor
410
448
Powder-Specific
Non-Linear Signal
Generator Module
450
Application
Programs
454
Data
451
Data
456
Operating
System
452
I/O Device
Drivers
458
Memory
414
Dispensing/
Inhaler
Delivery
System
420

FIG. 22

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| 60/440,513 | 16 January 2003 (16.01.2003) | US |

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(75) Inventors/Applicants *(for US only)*: **CROWDER, Timothy, M.** [US/US]; 1205 Hillsborough Road, Chapel Hill, NC 27516 (US). **HICKEY, Anthony, J.** [GB/US]; 1208 Killington Court, Chapel Hill, NC 27514 (US). **WARDEN, Jeffrey, A.** [US/US]; 12213 Dunard Street, Raleigh, NC 27614 (US).

(74) Agent: **MYERS BIGEL SIBLEY & SAJOVEC, P.A.**; P.O. Box 37428, Raleigh, NC 27627 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**
— *with international search report*

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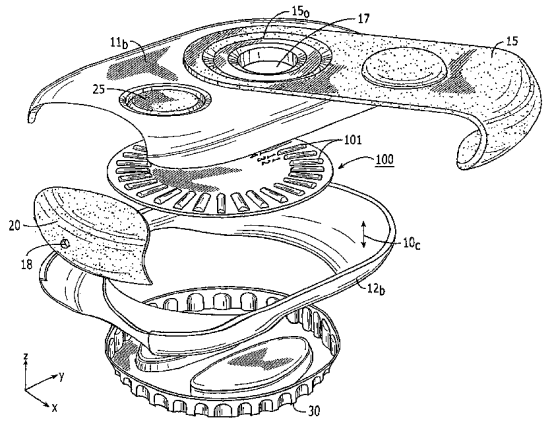
18 March 2004

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: DRY POWDER INHALERS FOR USE WITH PIEZOELECTRIC POLYMER-DRIVEN DELIVERY MEANS, AND ASSOCIATED BLISTER PACKAGE COMPRISING A PIEZOELECTRIC POLYMER MATERIAL




(57) Abstract: The present invention includes dry powder inhalers and associated multi-dose dry powder packages for holding inhalant formulated dry powder substances. The multi-dose package (100) comprises at least one thin piezoelectric polymer material layer (28) defining at least a portion of a plurality of spatially separated discrete elongate dry powder channels (101) having an associated length, width and height; and a metallic material (100m) attached to selected portions of the piezoelectric polymer material (28) including each of the regions corresponding to the elongate dry powder channels (101) to, in operation, define active energy releasing vibratory channels. In operation, the elongate channels can be selectively individually activated to vibrate upon exposure to an electrical input. The dry powder inhaler (10) includes an elongate body (10b) having opposing first and second outer primary surfaces (11, 12) with a cavity (10c) therebetween and a multi-dose sealed blister package (100) located in the said cavity (10c). The inhaler (10) also includes a cover member (15) that is pivotably attached to the elongate body (10b).

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# INTERNATIONAL SEARCH REPORT

Int ɔlication No
PCT/US 03/14619

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M A61J B65D B06B B05B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 01 68169 A (CROWDER TIMOTHY M ;UNIV NORTH CAROLINA (US); HICKEY ANTHONY J (US)) 20 September 2001 (2001-09-20) cited in the application<br><br>page 4, line 28-30<br>page 10, line 7-23<br>page 15, line 5 -page 16, line 32<br>page 18, line 3-11<br>page 19, line 22,23<br>page 25, line 28 -page 27, line 17<br>page 31, line 30 -page 32, line 3<br>figures 1,2,3A-3D<br>claims 50,51<br>---<br>-/-- | 1-4,6,<br>8-12,<br>20-28,<br>30,31,<br>62-67 |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 11 December 2003 | 23. 12. 03 |

| Name and mailing address of the ISA | Authorized officer |
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| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Azaïzia, M |

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# INTERNATIONAL SEARCH REPORT

Int ication No
PCT/US 03/14619

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | EP 1 106 196 A (ATSUGI UNISIA CORP ;DOTT LTD COMPANY (JP))<br>13 June 2001 (2001-06-13)<br>column 19, line 27 -column 23, line 50<br>figures 20-31 | 10,12,<br>23-26,28 |
| A | US 5 622 166 A (CAMERON ALLAN ET AL)<br>22 April 1997 (1997-04-22)<br>column 3, line 52 -column 4, line 17<br>figures 10-15 | 31 |
| A | EP 1 166 812 A (MICRODOSE TECHNOLOGIES INC) 2 January 2002 (2002-01-02)<br>column 6, line 44 -column 7, line 35<br>column 7, line 42-54<br>column 8, line 10-13<br>figures 1A,1B,2-5,6A,6B | 1,7,13 |
| X | EP 1 172 122 A (TECHNOLOGY PARTNERSHIP)<br>16 January 2002 (2002-01-16)<br>column 1, line 42-48<br>column 1, line 55 -column 2, line 9<br>column 3, line 4 -column 4, line 19<br>figures 1-4 | 32,<br>37-39,<br>42-45 |
| X | US 5 388 572 A (FOXEN THOMAS ET AL)<br>14 February 1995 (1995-02-14)<br>column 8, line 44 -column 11, line 22<br>figures 5-12C | 33-36 |
| X | EP 0 129 985 A (GLAXO GROUP LTD)<br>2 January 1985 (1985-01-02)<br>page 4, line 6 -page 5, line 16<br>figures 3-6 | 32 |
| A | US 4 778 054 A (NEWELL ROBERT E ET AL)<br>18 October 1988 (1988-10-18)<br>column 4, line 8 -column 5, line 4<br>column 5, line 27-68<br>figures 3,4,6,7 | 42,43 |
| A | US 5 921 237 A (HOLTON NELSON ET AL)<br>13 July 1999 (1999-07-13)<br>column 3, line 29-32<br>figure 5 | 45 |

# INTERNATIONAL SEARCH REPORT

[illegible] application No.
PCT/US 03/14619

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 68-94
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-13, 20-67

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1, 7-13, 20-28 and 31

   A multi-dose dry powder package with a plurality of specially designed elongated channels.

2. Claims: 2-6, 29 and 30

   A multi-dose dry powder package in combination with an input signal generating circuit.

3. Claims: 14-18

   Multi-dose dry powder packages held in proximately spaced stacked relationship during use.

4. Claim : 19

   A multi-dose dry powder package comprising a plurality of airflow and/or differential pressure sensors.

5. Claims: 32-61

   A dry powder inhaler comprising an elongated body.

6. Claims: 62-67

   A method for fabricating a multi-dose dry powder package.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]plication No
PCT/US 03/14619

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
|---|---|---|---|---|
| WO 0168169 A | 20-09-2001 | AU | 3110201 A | 24-09-2001 |
| | | BR | 0109127 A | 22-04-2003 |
| | | CA | 2400349 A1 | 20-09-2001 |
| | | CN | 1416357 T | 07-05-2003 |
| | | EP | 1267969 A1 | 02-01-2003 |
| | | JP | 2003526480 T | 09-09-2003 |
| | | NO | 20024311 A | 11-11-2002 |
| | | WO | 0168169 A1 | 20-09-2001 |
| EP 1106196 A | 13-06-2001 | JP | 2001161820 A | 19-06-2001 |
| | | JP | 2001161788 A | 19-06-2001 |
| | | EP | 1106196 A2 | 13-06-2001 |
| US 5622166 A | 22-04-1997 | US | 6328034 B1 | 11-12-2001 |
| | | AU | 695051 B2 | 06-08-1998 |
| | | AU | 5251096 A | 18-11-1996 |
| | | BG | 62921 B1 | 30-11-2000 |
| | | BG | 101992 A | 31-07-1998 |
| | | BR | 9608194 A | 21-07-1998 |
| | | CA | 2217672 A1 | 31-10-1996 |
| | | CN | 1181709 A | 13-05-1998 |
| | | CZ | 9703349 A3 | 14-01-1998 |
| | | EP | 0835147 A1 | 15-04-1998 |
| | | HU | 9801656 A2 | 28-10-1998 |
| | | IL | 117706 A | 30-11-1999 |
| | | JP | 10512788 T | 08-12-1998 |
| | | NO | 974910 A | 24-10-1997 |
| | | NZ | 304654 A | 28-01-1999 |
| | | PL | 322909 A1 | 02-03-1998 |
| | | RO | 115407 B1 | 28-02-2000 |
| | | RU | 2162717 C2 | 10-02-2001 |
| | | SK | 144697 A3 | 04-03-1998 |
| | | TW | 384225 B | 11-03-2000 |
| | | US | 2002040713 A1 | 11-04-2002 |
| | | WO | 9633759 A1 | 31-10-1996 |
| | | US | 5921237 A | 13-07-1999 |
| | | US | 6029663 A | 29-02-2000 |
| | | AU | 729272 B2 | 01-02-2001 |
| | | AU | 3646697 A | 10-02-1998 |
| | | BR | 9710880 A | 17-08-1999 |
| | | CZ | 9900189 A3 | 12-05-1999 |
| | | EP | 0925084 A1 | 30-06-1999 |
| | | HU | 9903819 A2 | 28-03-2000 |
| | | JP | 2001507949 T | 19-06-2001 |
| | | NO | 990272 A | 22-03-1999 |
| | | NZ | 333685 A | 29-09-2000 |
| | | NZ | 505722 A | 30-03-2001 |
| | | WO | 9803217 A1 | 29-01-1998 |
| EP 1166812 A | 02-01-2002 | EP | 1166812 A1 | 02-01-2002 |
| | | US | 2002078947 A1 | 27-06-2002 |
| EP 1172122 A | 16-01-2002 | EP | 1172122 A1 | 16-01-2002 |
| | | WO | 0205881 A1 | 24-01-2002 |
| US 5388572 A | 14-02-1995 | AU | 7393994 A | 22-05-1995 |
| | | BR | 9407893 A | 19-11-1996 |
| | | CA | 2157583 A1 | 04-05-1995 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible] cation No
PCT/US 03/14619

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 5388572 A | | CN 1120812 A | 17-04-1996 |
| | | EP 0732951 A1 | 25-09-1996 |
| | | FI 954099 A | 01-09-1995 |
| | | JP 9504455 T | 06-05-1997 |
| | | NO 953427 A | 09-10-1995 |
| | | WO 9511715 A1 | 04-05-1995 |
| EP 0129985 A | 02-01-1985 | AT 36965 T | 15-09-1988 |
| | | AU 569743 B2 | 18-02-1988 |
| | | AU 2852384 A | 29-11-1984 |
| | | CA 1238251 A1 | 21-06-1988 |
| | | DE 3473834 D1 | 13-10-1988 |
| | | DK 253584 A | 25-11-1984 |
| | | EP 0129985 A1 | 02-01-1985 |
| | | ES 8600947 A1 | 16-02-1986 |
| | | FI 842052 A ,B, | 25-11-1984 |
| | | GB 2142246 A ,B | 16-01-1985 |
| | | IE 55508 B1 | 10-10-1990 |
| | | IL 71852 A | 31-08-1988 |
| | | IN 163009 A1 | 30-07-1988 |
| | | JP 59225070 A | 18-12-1984 |
| | | KR 9104328 B1 | 26-06-1991 |
| | | MY 86187 A | 31-12-1987 |
| | | NO 842049 A ,B, | 26-11-1984 |
| | | NZ 208256 A | 31-03-1987 |
| | | ZA 8403878 A | 24-12-1984 |
| US 4778054 A | 18-10-1988 | AT 396333 B | 25-08-1993 |
| | | AT 357683 A | 15-12-1992 |
| | | AU 570013 B2 | 03-03-1988 |
| | | AU 1997783 A | 12-04-1984 |
| | | AU 584535 B2 | 25-05-1989 |
| | | AU 8315587 A | 21-04-1988 |
| | | BE 897946 A1 | 09-04-1984 |
| | | BR 8305562 A | 15-05-1984 |
| | | CA 1224992 A1 | 04-08-1987 |
| | | CA 1236736 A2 | 17-05-1988 |
| | | CH 662277 A5 | 30-09-1987 |
| | | CY 1477 A | 21-07-1989 |
| | | CY 1478 A | 21-07-1989 |
| | | DE 3336486 A1 | 26-04-1984 |
| | | DE 3348370 C2 | 11-10-2001 |
| | | DK 45198 A | 20-12-1999 |
| | | DK 464383 A | 09-04-1984 |
| | | ES 286422 U | 01-02-1986 |
| | | FI 833641 A ,B, | 09-04-1984 |
| | | FI 891175 A ,B, | 13-03-1989 |
| | | FR 2550452 A1 | 15-02-1985 |
| | | FR 2570607 A1 | 28-03-1986 |
| | | GB 2129691 A ,B | 23-05-1984 |
| | | GB 2169265 A ,B | 09-07-1986 |
| | | GR 79615 A1 | 31-10-1984 |
| | | HK 67689 A | 01-09-1989 |
| | | HK 67789 A | 01-09-1989 |
| | | IE 56059 B1 | 10-04-1991 |
| | | IE 56060 B1 | 10-04-1991 |
| | | IL 69932 A | 31-12-1987 |
| | | IL 80468 A | 30-11-1987 |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[illegible]plication No
PCT/US 03/14619

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| US 4778054 A | | IN 160851 A1 | 08-08-1987 |
| | | IT 1203660 B | 15-02-1989 |
| | | JP 59088158 A | 22-05-1984 |
| | | JP 1888266 C | 07-12-1994 |
| | | JP 5076872 B | 25-10-1993 |
| | | JP 5200100 A | 10-08-1993 |
| | | KE 3860 A | 02-06-1989 |
| | | KE 3861 A | 02-06-1989 |
| | | KR 9102248 B1 | 08-04-1991 |
| | | LU 85034 A1 | 19-06-1985 |
| | | NL 8303461 A ,B, | 01-05-1984 |
| | | NL 9700002 A ,B, | 02-06-1997 |
| | | NO 833667 A ,B, | 09-04-1984 |
| | | NZ 205892 A | 31-07-1987 |
| | | NZ 218860 A | 26-04-1989 |
| | | PT 77471 A ,B | 01-11-1983 |
| | | SE 458824 B | 16-05-1989 |
| | | SE 8305542 A | 09-04-1984 |
| | | SE 465752 B | 28-10-1991 |
| US 5921237 A | 13-07-1999 | US 5622166 A | 22-04-1997 |
| | | US 6328034 B1 | 11-12-2001 |
| | | AU 729272 B2 | 01-02-2001 |
| | | AU 3646697 A | 10-02-1998 |
| | | BR 9710880 A | 17-08-1999 |
| | | CA 2261172 A1 | 29-01-1998 |
| | | CZ 9900189 A3 | 12-05-1999 |
| | | EP 0925084 A1 | 30-06-1999 |
| | | HU 9903819 A2 | 28-03-2000 |
| | | JP 2001507949 T | 19-06-2001 |
| | | NO 990272 A | 22-03-1999 |
| | | NZ 333685 A | 29-09-2000 |
| | | NZ 505722 A | 30-03-2001 |
| | | US 2002040713 A1 | 11-04-2002 |
| | | WO 9803217 A1 | 29-01-1998 |
| | | AU 695051 B2 | 06-08-1998 |
| | | AU 5251096 A | 18-11-1996 |
| | | BG 62921 B1 | 30-11-2000 |
| | | BG 101992 A | 31-07-1998 |
| | | BR 9608194 A | 21-07-1998 |
| | | CA 2217672 A1 | 31-10-1996 |
| | | CN 1181709 A | 13-05-1998 |
| | | CZ 9703349 A3 | 14-01-1998 |
| | | EP 0835147 A1 | 15-04-1998 |
| | | HU 9801656 A2 | 28-10-1998 |
| | | IL 117706 A | 30-11-1999 |
| | | JP 10512788 T | 08-12-1998 |
| | | NO 974910 A | 24-10-1997 |
| | | NZ 304654 A | 28-01-1999 |
| | | PL 322909 A1 | 02-03-1998 |
| | | RO 115407 B1 | 28-02-2000 |
| | | RU 2162717 C2 | 10-02-2001 |
| | | SK 144697 A3 | 04-03-1998 |
| | | TW 384225 B | 11-03-2000 |
| | | WO 9633759 A1 | 31-10-1996 |
| | | US 6029663 A | 29-02-2000 |